

SCIENCE CAPSULES

Gene Therapy May Prevent Damage From Stroke. Hemorrhagic strokes are devastating not only because of their initial damage to the brain, but also because of damage from subsequent strokes that occur when the pooled blood causes blood vessels to constrict. Researchers studying an animal model of stroke transferred the gene for the vasodilator calcitonin gene-related peptide into animals via the cerebrospinal fluid and observed its effects on arteries in the brain. The peptide prevented constriction of brain blood vessels, thereby preventing subsequent strokes. If successful in patients, the approach could save countless lives annually and tens of millions of dollars in hospitalization and rehabilitative nursing care costs. [secondary – treatment]

Toyoda K, Faraci FM, Watanabe Y, Ueda T, Andresen JJ, Chu Y, Otake S, and Heistad DD: Gene transfer of calcitonin gene-related peptide prevents vasoconstriction after subarachnoid hemorrhage. Circulation Research 87: 818-824, 2000.

Identifiable Illnesses from Hepatitis C Virus (HCV) Infection Take Many Years to Develop. Although chronic HCV infection can lead to serious complications including cirrhosis and hepatocellular carcinoma, early symptoms of infection are usually mild or non-existent. Researchers following people who contracted transfusion-associated HCV approximately 25 years ago determined that hepatitis C progresses slowly in most, but not all, infected persons. While more than half of the patients died from causes unrelated to infection and several died from HCV-associated liver damage, the conditions of the remaining ranged from spontaneous and complete recovery to moderately impaired liver function to severe liver disease. The next challenges are to identify factors that influence the course of hepatitis C infection in these and other study populations, and to define markers that predict the severity of outcomes for the approximately 4 million HCV-infected people in the United States.

Seeff LB, Hollinger FB, Alter HJ, Wright EC, Cain CMB, Buskell ZJ, Ishak KG, Iber FL, Toro D, Samanta A, Koretz RL, Perrillo RP, Goodman ZD, Knodell RG, Gitnick G, Morgan TR, Schiff ER, Lasky S, Stevens C, Vlahcevic RZ, Weinshel E, Tanwandee T, Lin HJ, and Barbosa L: Long-term mortality and morbidity of transfusion-associated non-A, non-B, and type C hepatitis: A National Heart, Lung, and Blood Institute collaborative study. Hepatology 33: 455-463, 2001.

Where We Live Affects Our Cardiovascular Health. Researchers found that living in a disadvantaged neighborhood is associated with an increased incidence of coronary heart disease (CHD). This relationship persisted even after income, education, occupation, and other CHD risk factors were taken into account. A variety of neighborhood characteristics may contribute to CHD risk, including the availability of resources and services to promote or maintain healthy lifestyles, the physical environment of a community, the presence of numerous chronic stressors such as noise or violence, and the social norms and support systems. Therefore, interventions that improve neighborhoods by increasing the availability of healthful foods and recreational facilities, decreasing tobacco advertising, or conducting other activities that facilitate adoption of

a healthy lifestyle, could reduce geographic and socioeconomic disparities in CHD incidence. [secondary – prevention]

Diez Roux AV, Merkin SS, Arnett D, Chambless L, Massing M, Nieto FJ, Sorlie P, Szklo M, Tyroler HA, and Watson RL: Neighborhood of residence and incidence of coronary heart disease. The New England Journal of Medicine 345: 99-106, 2001.

“Early to Bed, Early to Rise” Gene Discovered. People with advanced sleep phase syndrome (ASPS) tend to fall asleep in the early evening and awake in the wee hours of the morning after a normal sleep duration. Investigators studying a large family with ASPS recently found a mutation in the *hPer2* gene that affects the accumulation of proteins that regulate the body’s biological clock. By providing insight into the complex interaction between the biological clock and its regulators, this discovery will contribute to better understanding and treatment of ASPS, as well as of sleep disturbances associated with aging, jet lag, and shift work.

Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup :DM, Ptacek LJ and Fu YH: An *hPer2* phosphorylation site mutation in familial advanced sleep phase syndrome. *Science* 291: 1040-1043, 2001.

Researchers Uncover a Secret of Burning Fat. Researchers recently discovered that perilipin, a protein associated with fat metabolism and weight gain in mice and humans, acts by preventing a “fat-burning” enzyme from entering cells where it can break down fat molecules and convert them to energy. They also showed that mice whose perilipin genes had been inactivated had about half as much body fat, eight percent more muscle, and higher metabolic rates than normal mice, despite eating 25 percent more food. Even mice that had been genetically programmed to be obese grew up to be lean and healthy when the perilipin gene was turned off. Since perilipin appears to be found only on the surface of fat cells, researchers are hopeful that new antiobesity drugs could be developed to work exclusively on adipose tissues without causing side effects in other tissues. [secondary – treatment]

Martinez-Botas J, Anderson JB, Tessier D, Lapillonne A, Chang BH, Quast MJ, Gorenstein D, Chen KH, and Chan L: Absence of perilipin results in leanness and reverses obesity in *Lep^{db/db}* mice. Nature Genetics 26: 474-479, 2000.

Understanding Bacterial Interactions has Potential to Help Cystic Fibrosis Patients.

Pseudomonas aeruginosa is a life-threatening bacterium that colonizes in the lungs of most children with cystic fibrosis and causes extensive tissue damage and, eventually, respiratory failure. Once established, the colonies are resistant to antibiotics. Now, researchers have learned that the innate antibiotic resistance occurs because *P. aeruginosa* bacteria aggregate in layers, forming a biofilm that shelters them from antibiotics and the immune system. By understanding how bacteria interact with one another to form layers and how layering leads to drug resistance, scientists hope to be able to develop interventions that will render the bacteria susceptible to antibiotics. [secondary – treatment]

Singh PK, Schaefer AL, Parsek MR, Moninger TO, Welsh MJ, and Greenberg EP: Quorum-sensing signals indicate that cystic fibrosis lungs are infected with bacterial biofilms. Nature 407: 762-764, 2000.

Sensitivity to Salt Increases Risk of Early Death. Although people with high blood pressure have been advised for years to reduce the salt in their diets, salt also appears to be shortening the lives of people without hypertension. A study monitoring approximately 700 people who had their blood pressure and its response to salt intake evaluated 27 years ago has provided some unexpected results: salt sensitivity (an exaggerated response of blood pressure to salt intake) increases risk of premature death not only in men and women with elevated blood pressure but, surprisingly, also in those with normal blood pressure. Because there is no easy way to test for salt sensitivity, this study provides yet one more reason why even people with normal blood pressure should be careful about their salt intake. [secondary – prevention]

Weinberger MH, Fineberg NS, Fineberg SE, and Weinberger M: Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. Hypertension 37: 429-432, 2001.

Gene Therapy Against Free Radicals May Prevent Vascular Damage. Reactive oxygen molecules, also known as “free radicals,” contribute to blood vessel injuries that occur during atherosclerosis, restenosis (closure of an artery after it has been opened by angioplasty), and graft failure following coronary artery bypass surgery. To counter damage from free radicals, researchers used gene therapy to stimulate production of an enzyme called heme oxygenase-1, which, they subsequently demonstrated, protects against vascular constriction and excessive growth in response to injury. The results suggest that gene therapy techniques that produce heme oxygenase-1 may be useful not only in treating vascular diseases and preventing restenosis, but also for reducing vasoconstriction during strokes. [secondary – treatment]

Duckers HJ, Boehm M, True AL, Yet SF, San H, Park JL, Webb RC, Lee ME, Nabel GJ, and Nabel EG: Heme oxygenase-1 protects against vascular constriction and proliferation. Nature Medicine 7: 693-698, 2001.

Factors Influencing Lung Development and Injury Identified. Bronchopulmonary dysplasia (BPD) is a consequence of disrupted lung development and affects more than 10,000 premature infants each year. Investigators studying bombesin-like peptide (BLP), a molecule that is over-produced in infants with BPD, discovered that different forms of the peptide are produced when fetal lungs are exposed to different traumas and that antibodies against BLP can prevent development of BPD. They also found that corticotropin-releasing hormone (CRH), a substance produced by fetal lung tissue, stimulates lung development. Although much needs to be understood before any therapy for BPD could be tested in premature infants, the gap is beginning to close between what is known about lung development and what constitutes therapeutic opportunities for this particularly vulnerable patient population. [secondary – treatment]

Cullen A, Emanuel RL, Torday JS, Asokanathan N, Sikorski KA, and Sunday ME: Bombesin-like peptide and receptors in lung injury models: diverse gene expression, similar function. Peptides 21: 1627-1638, 2000.

Emanuel RL, Torday JS, Asokanathan N, and Sunday ME: Direct effects of corticotropin-releasing hormone and thyrotropin-releasing hormone on fetal lung explants. Peptides 21: 1819-1829, 2000.

The Impact of Family Help on the Timing of Placement of Cognitively Impaired Elders in an Institution. Various factors, including incontinence, disruptive and/or abusive behaviors often lead to the decision to place a family member with Alzheimer's disease in an institution. Family support for the primary caregiver is one factor thought to delay placement. The results of this study showed that the total hours of family help were not highly related to the timing of nursing home placement, but specific types of help effectively delayed placement. Specifically, this study found that caregivers who received help with the elderly relative's Activities of Daily Living (e.g., eating, dressing, bathing, toileting) needs and help with overnight care were much more likely to postpone institutionalization.

Gaugler JE, Edwards AB, Femia EE, Zarit SH, Stephens MAP, Townsend A, and Greene R: Predictors of institutionalization of cognitively impaired elders: family help and the timing of placement. Journal of Gerontology: Psychological Sciences 55B: 247-255, 2000.

Decline in Severe Cognitive Impairment Among Older Americans. Several recent studies have reported declines in the rates of physical disability and functional limitations among older Americans during the 1980s and 1990s. It was not known, however, whether there was a similar decline in the rates of cognitive impairment. In a study of non-institutionalized Americans ages 70 and older, researchers detected a decline in the proportion of older persons with severe cognitive impairment during the 1990s that was similar to that reported for physical disability and functional limitations. Tracking changes in cognitive impairment in older populations can provide insight into the need for and costs of services and interventions.

Freedman VA, Aykan H, and Martin LG: Aggregate changes in severe cognitive impairment among older Americans: 1993 and 1998. Journal of Gerontology: Social Sciences 56B: S100-S111, 2001.

Freedman VA, Aykan H, and Martin LG: Another look at aggregate changes in severe cognitive impairment: further investigation into the cumulative effects of three survey design issues. Journal of Gerontology: Social Sciences (in press 2001).

Comorbidity and Breast Cancer in Older Women. Most breast cancer cases and breast cancer related deaths occur in women aged 55 years and older. Concurrent age-related health problems such as hypertension, heart disease, diabetes, chronic obstructive pulmonary disease, and cerebrovascular disease are likely to affect the cancer course and treatment options. It was found that older breast cancer patients with preexisting health conditions receive less aggressive pretreatment assessments and cancer treatment than women who are younger and healthier. Given the high incidence and mortalities of breast cancer in postmenopausal women, additional research is needed to determine how age differences and accompanying health problems should guide assessment and treatment choices.

Yancik R, Wesley MN, Ries LAG, Havlik RJ, Edwards BK, and Yates JW: Effect of Age and Comorbidity in Postmenopausal Breast Cancer Patients Aged 55 Years and Older. Journal of the American Medical Association 285: 885-892, 2001.

Aortic Stiffness and Visceral Adiposity in Older Adults Enrolled in Health ABC. As people age, their arteries stiffen, resulting in higher systolic blood pressure. Structural changes occur, including thickening of the arterial wall. Arterial stiffening progresses at different rates for different individuals. Accelerated arterial stiffening has been linked to diabetes, and insulin resistance may promote arterial stiffening independent of age. Weight and body fat distribution are also related to arterial stiffness. The study of Health, Aging, and Body Composition is a population based prospective study of the impact of weight and body composition on age-related physiologic and functional changes. Among healthy older individuals in this study, measures of body weight and degree of fat correlated with greater vascular stiffness, and the strongest association was with abdominal visceral fat. The association between visceral fat and aortic stiffening may be mediated through a syndrome involving insulin resistance. Keeping weight (specifically visceral fat) within normal limits through the advancing years may slow the process of vascular aging, possibly reducing the associated risks of heart disease and stroke.

Sutton-Tyrrell K, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, Spurgeon H, and Vaitkevicius P: For the health ABC investigators: aortic stiffness is associated with visceral adiposity in older adults enrolled in health ABC. Hypertension (in press 2001).

Cardiovascular Disease, Interleukin-6, and Risk of Mortality in Older Women. The presence and severity of chronic disease conditions may explain the association between elevated circulating markers of inflammation and the risk of mortality. Systemic chronic inflammation has been found to be related to all-cause mortality risk in older persons, but the underlying mechanisms are not fully understood. Interleukin-6 (IL-6) is a marker of inflammation and was measured in women enrolled in the Women's Health and Aging Study, a prospective study of the causes and course of disability among moderately to severely disabled older women living in the community. Findings from a survey conducted over a 3-year follow-up confirmed that serum IL-6 level is helpful in identifying a subgroup of older women with cardiovascular disease who are at high risk of death. Although IL-6 was not specifically related to cardiovascular mortality, these results suggest that the relation with mortality is not explained simply by the presence and severity of other existing diseases and that systemic inflammation, as measured by serum IL-6, may be related to a poorer clinical outcomes in women with cardiovascular disease.

Volpato S, Guralnik JM, Ferrucci L, Balfour J, Chaves P, Fried LP, and Harris TB: Cardiovascular disease, interleukin-6, and risk of mortality in older women: The Women's Health and Aging Study. Circulation 103: 947-953, 2001.

Importance of Local Estrogen Biosynthesis in Improved Cardiovascular Function.

Estrogen appears to protect women from atherosclerosis during their reproductive years, while loss of estrogen after menopause appears to increase their risk. Androgens are thought to confer an increased risk of atherosclerosis and are associated with increased lipid-associated risk factors, particularly in several animal models on high cholesterol diets. However, recent studies in mice show cardio-protective effects for testosterone. Cardiovascular tissue appears to be able to convert testosterone to estrogen, so testosterone may in fact play a protective role against cardiovascular disease. In this study, testosterone attenuated early atherogenesis in castrated mice, most likely through conversion to estrogen in walls of blood vessels. Local estrogen production, whether in cardiac, bone, or brain tissue, may provide sufficient protection directly at the sites where needed, and thus avoid the need for systemic estrogen treatments, which may create an increased risk for adverse health events such as breast cancer.

Nathan L, Shi W, Dinh H, Mukherjee TK, Wang X, Lusis AJ, and Chaudhuri C: Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. Proceedings of the National Academy of Sciences USA 98: 3589-3593, 2001.

Caloric Restriction Has No Adverse Effects on Skeletal and Reproductive Health in Rhesus Monkeys. The loss of bone mass with aging and following menopause is a major health problem in the U.S. Caloric restriction (CR), significantly reducing calories while maintaining adequate nutrition, has been shown to retard many physiological processes of aging in rodents. Yet based on studies in rodents, there also have been concerns that caloric restriction could result in bone loss and could disrupt reproductive cycling. These findings may have important implications in potential human trials of CR or CR-like interventions. In recent studies in non-human primates, investigators looked at bone mass and biochemical markers of skeletal health and reproductive cycling in rhesus monkeys that had been on CR for several years. They found that CR does not adversely alter bone or reproductive health in primates. These data suggest that consumption of a nutritionally adequate diet during and following weight loss may help to protect the skeleton from potential adverse effects of reduced calorie intake.

Lane MA, Black A, Handy AM, Shapses SA, Tilmont EM, Kiefer TL, Ingram DK, and Roth GS: Energy restriction does not alter bone mineral metabolism or reproductive cycling and hormones in female rhesus monkeys. Journal of Nutrition 13: 820-827, 2001.

Black A, Allison DB, Shapses SA, Tilmont, EM, Handy AM, Ingram DK, Roth GS, and Lane MA: Calorie restriction and skeletal mass in rhesus monkeys (*Macaca mulatta*): evidence for an effect mediated through changes in body size. Journal of Gerontology 56A: B1-B10, 2001.

Familial Patterns and Protective Factors in Exceptional Longevity. The role of genetic factors in determining longevity has been assessed in families with a history of exceptional survival to old age. A recent study of four families with a high number of members surviving to 90 years or more found evidence of a familial cluster of longevity than cannot be explained by chance alone, lending strong support to the idea that genetic factors may contribute to exceptional longevity. A second study found that exceptionally long-lived persons may pass on to their children lifelong protection against major diseases of aging, including an exceptionally good pattern of circulating cholesterol, a major factor affecting risk of cardiovascular disease.

Improved understanding of genetic and other factors that contribute to long life may lead to new ways to identify risk factors for age-related diseases and disabilities, prevent them, and extend healthy life.

Perls T, Shea-Drinkwater M, Bowen Flynn J, Ridge SB, Kang S, Joyce E, Daly M, Brewster SJ, Kunkel L, and Puca AA: Exceptional familial clustering for extreme longevity in humans. Journal of the American Geriatrics Society 48: 1483-1485, 2000.

Barzilai N, Gabriely J, Gabriely M, Ienkowitz N, and Sorkin JD: Offspring of centenarians have a favorable lipid profile. Journal of the American Geriatrics Society 49: 1-4, 2001.

Chromosome 10 Contains New Risk Factor Genes for Late Onset Alzheimer's Disease. It is important to identify which of the 30,000 or so genes in the human genome can affect the development of Alzheimer's disease (AD) pathology. Until this year, just four genes were conclusively known to do this. Three of these genes are associated with early onset AD, and only one is associated with the more common form of the disease, late-onset AD (LOAD). Recently, geneticists have suggested that as many as four additional, and as yet unidentified, genes may also be risk factors for LOAD. Three recent studies indicate that there may be as many as two novel LOAD gene loci on the long arm of chromosome 10. Finding new risk factor genes will help identify pathways affecting the development or progression of AD and may eventually lead to better predictors of the disease even before it is diagnosed.

Bertram L, Blacker D, Mullin K, Keeney D, Jones J, Basu S, Yhu S, McInnis MG, Go RCP, Vekrellis K, Selkoe DJ, Saunders AJ, and Tanzi RE: Evidence for genetic linkage of Alzheimer's disease to chromosome 10q. Science 290: 2302-2303, 2000.

Ertekin-Taner N, Graff-Radford N, Younkin LH, Eckman C, Baker M, Adamson J, Ronald J, Blangero J, Hutton M, and Younkin SG: Linkage of plasma A42 to a quantitative locus on chromosome 10 in late-onset Alzheimer's disease pedigrees. Science 290: 2303-2304, 2000.

Myers A, Holmans P, Marshall H, Kwon J, Meyer D, Ramic D, Shears S, Booth J, DeVrieze FW, Crook R, Hamshere M, Abraham R, Tunstall N, Rice F, Carty S, Lillystone S, Kehoe P, Rudrasingham V, Jones L, Lovestone S, Perez Tur J, Williams J, Owen MJ, Hardy J, and Goate AM: Susceptibility locus for Alzheimer's disease on chromosome 10. Science 290: 2304-2305, 2000.

RANTES Potentiates Antigen-Specific Peripheral and Mucosal Immune Responses. Over the past 15 years, members of a family of molecules called *chemokines* have been shown to be involved in immune responses in both humans and rodents. Chemokines play important roles in autoimmune, inflammatory, stress and trauma-based injuries. Researchers have now investigated the possibility that chemokines might improve the effectiveness of vaccines. Since elderly subjects show a diminished capacity to respond to a variety of vaccines, discovering new and novel substances that enhance the immune response is a vital area of research. Researchers discovered that a chemokine called RANTES, when given to mice with a vaccine, enhanced the immune response to the vaccine. Antibody levels were enhanced in both serum and mucosal secretions, which may be important to defenses against infection. These studies support the possible use of chemokines as additives to vaccine preparations, to facilitate vaccine responses in patients with lowered immune responses and elderly people.

Lillard JW Jr, Boyaka PN, Taub DD, and McGhee JR: RANTES potentiates antigen-specific mucosal immune responses. Journal of Immunology 166: 162-169, 2001.

Old and Young Humans Produce Similar Types of Antibodies. The production of antibodies by B lymphocytes is an important component of the immune response to antigens in infectious microbes or vaccine preparations. One mechanism involved in these responses involves a high frequency of mutations (somatic hypermutation) in the genes encoding antibodies, creating new antibody products with potential for increased strength of binding to the immunizing antigen. The ability to undergo somatic hypermutation is thus a potentially important component of effective antibody responses. To determine whether aging alters the frequency and pattern of hypermutation of antibody genes, mutated genes from young and old humans were sequenced and compared. There were more mutated genes in the young population compared to the old population, indicating that somatic hypermutation declines with age. However, among the mutated genes, the frequency, location, and types of substitutions were similar between the young and old groups. Furthermore, the ratio of replacement to silent mutations was much higher in the antibodies from old people, which indicates that B cells expressing mutated antibodies had been selected during responses to antigen. This suggests that humans should be able to respond to antigenic challenges with effective antibody responses well into old age.

Rosner K, Winter DB, Kasmer C, Skovgaard GL, Tarone RE, Bohr VA, and Gearhart PJ: Impact of age on hypermutation of immunoglobulin variable genes in humans. Journal of Clinical Immunology 21: 102-115, 2001.

Protein Switching Between Inactive and Active States. Structures of biological macromolecules are often presented as static images, but proteins and nucleic acids are in constant motion. The motions of a protein are an important part of its activity – movement is essential for the binding and release of ligands by receptors and for the catalytic activity of enzymes. However, assessing the interrelationships among a protein's motions, activity, and structure has been problematic because it is often difficult to observe all three characteristics simultaneously. Scientists recently have used nuclear magnetic resonance (NMR) spectroscopy to correlate the structural states of an important signaling molecule and its motions directly with biochemical activity. Such studies hold great promise for deciphering how motions influence the function of proteins.

Volkman BF, Lipson D, Wemmer DE, and Kern D: Two-state allosteric behavior in a single-domain signaling protein. Science 291: 2429-2433, 2001.

Buck M, and Rosen MK: Structural biology: flipping a switch. Science 291: 2329-2330, 2001.

Largest Membrane Protein Domain (19kDa) Determined by Solution NMR. Nuclear magnetic resonance (NMR) spectroscopy was used to determine the structure of the transmembrane domain of membrane protein A in *e. coli*. The structure was similar to that obtained in previous studies using x-ray crystallographic methods, but the results of this study demonstrate the ability of NMR to shed more light on structure and function by measuring conformational changes associated with changing states of the protein.

Arora A, Abildgaard F, Bushweller JH, and Tamm LK: Structure of outer membrane protein A transmembrane domain by NMR spectroscopy. Nature Structural Biology 8: 334-338, 2001.

Key Mechanics of Cell Membrane Fusion Revealed. Scientists supported by NIH have developed a new working model of cell membrane fusion. This model will be useful for studying the biophysics of a process that is fundamental to all life. It also could help enhance development of fusion-blocking agents aimed at preventing infection by HIV, influenza, Ebola, and other viruses which use membrane fusion machinery to enter cells. [secondary – treatment]

Haque ME, McIntosh TJ, and Lentz BR: Influence of lipid composition on physical properties and PEG-mediated fusion of curved and uncurved model membrane vesicles: nature's own fusogenic lipid bilayer. Biochemistry 40: 4340-4348, 2001.

On the Way to Making a Pancreas. Research supported by NIH shows that, under certain conditions, cells which develop into the liver can also give rise to part of the pancreas. Understanding how these conditions – signaling and gene regulatory factors – control the development of the liver and pancreas should provide important insights into how to control the differentiation of life-threatening cells which surface during carcinogenesis, chronic tissue damage, and metabolic diseases. [secondary – treatment]

Deutsch G, Jung J, Zheng M, Lora J, and Zaret KS: A bipotential precursor population for pancreas and liver within the embryonic endoderm. Development 128: 871-881, 2001.

Drosophila Study Implicates New Genes in Human Neurodegenerative Disorders. The *SCA1* gene is involved in Spinocerebellar ataxia type 1 (SCA1), one of a group of hereditary neurological disorders that includes Huntington disease. Research on the role of the *SCA1* gene in SCA1 resulted in the unexpected finding that there are several other genes involved in *SCA1*-induced neurodegeneration which have not previously been implicated in these diseases. These findings should lead to a better understanding of the pathogenesis of these disorders and aid in the search for treatments. [secondary – treatment]

Fernandez-Funez P, Nino-Rosales ML, de Gouyon B, She W, Luchak JM, Martinez P, Turiegano E, Benito J, Capovilla M, Skinner PJ, McCall A, Canal I, Orr HT, Zoghbi HY, and Botas J: Identification of genes that modify ataxin-1-induced neurodegeneration. Nature 408: 101-106, 2000.

Sleepy Genes. Researchers have identified a gene that encodes regulatory factors in areas of the brain associated with circadian rhythms, the sleep/wake cycle, and other processes and behaviors mediated by homeostatic systems. Discovery of the gene and subsequent research to characterize its products have led to a much better understanding of the sleep disorder narcolepsy, and provide new opportunities for the development of treatments. [secondary – treatment]

Bourgin P, Huitron-Resendiz S, Spier AD, Fabre V, Morte B, Criado JR, Sutcliffe JG, Henriksen SJ, and de Lecea L: Hypocretin-1 modulates rapid eye movement sleep through activation of locus coeruleus neurons. Journal of Neuroscience 20: 7760-7765, 2000.

Controlling Zinc in Cells. Inorganic elements such as zinc, copper, and iron are vital to the healthy functioning of cells in living organisms. For example, each cell in the human body requires an enormous amount of zinc. Through NIH-supported research, chemists have acquired new insight into how zinc pumps and their regulatory proteins function in cells. These findings should improve our knowledge of diseases related to zinc metabolism and influence future drug design and pharmaceuticals. [secondary – treatment]

Outten CE, and O'Halloran TV: Femtomolar sensitivity of metalloregulatory proteins controlling zinc homeostasis. Science 292: 2488-2492, 2001.

Discovery of a Key Step in Auxin Biosynthesis through Comparative Biochemistry.

Research conducted in 1997 helped identify defects in human flavin monooxygenase-3 (FMO-3) as the genetic basis in the inherited metabolic disorder trimethylaminuria. However, the physiological functions of FMO-3 remain unclear. Current research supported by NIH has identified a key role played by a FMO-like family of enzymes in the biosynthesis of the growth hormone auxin in plants such as *Arabidopsis*. This work is providing clues that can be used to clarify the physiological roles of mammalian counterparts to the FMO-like genes found in *Arabidopsis*. [secondary – treatment]

Zhao Y, Christensen SK, Fankhauser C, Cashman JR, Cohen JD, Weigel D, and Chory J: A role for flavin monooxygenase-like enzymes in auxin biosynthesis. Science 291: 306-309, 2001.

Characterization of the Control of Telomeres in Drosophila. Telomeres are the DNA and protein structures present at the ends of chromosomes. These specialized structures are involved in the replication and stability of linear DNA molecules. Their proper functioning is vital to cell growth and the proper segregation of chromosomes to daughter cells. In *Drosophila*, telomeric repeat arrays consist of non-long terminal repeat retrotransposons, primarily HeT-A, attached to the chromosome end. Retrotransposons are segments of DNA generated using an RNA template that can move to different positions in the genome of a single cell. About 40 percent of the entire human genome consists of retrotransposons. HeT-A transposition normally occurs with a frequency sufficient to balance the loss of DNA from the chromosome end due to incomplete replication. Two mutations have been discovered that influence the frequency of HeT-A addition onto a chromosome end. One completely eliminates HeT-A additions while the other increases the frequency about 100 fold. These mutations are being used to investigate the mechanism of telomere length maintenance in *Drosophila*.

Mason JM, Haoudi A, Konev AY, Kurenova E, Walter MF, and Biessmann H: Control of telomere elongation and telomeric silencing in *Drosophila melanogaster*. Genetica 109: 61-70, 2000.

Insight into How Clots are Dissolved. Fibrinolysis is a process by which the body dissolves blood clots. A variety of molecular events are involved in this process, many of which remain to be identified. A particular metabolizing enzyme, CYP2J2, is abundant in the heart and blood

vessels and is responsible for creating a series of compounds called epoxyeicosatrienoic acids (EETs). The EETs play important roles in protecting the heart and blood vessels from damage. Scientists have now discovered that a particular EET also has a role in fibrinolysis and plays an important role in regulating vascular hemostasis.

Node K, Ruan XL, Dai J, Yang SX, Graham L, Zeldin DC, and Liao JK: Induction of tissue-type plasminogen activator expression by cytochrome P450 epoxygenase-derived eicosanoids. Journal of Biological Chemistry 276: 15983-15989, 2001.

Effect of Normal and Mutant MARCKS Protein on Cell Adhesion: Evidence for a Role in Brain Development. MARCKS protein (the name for a specific protein characterized as a “myristoylated alanine-rich C-kinase substrate”) has been shown to be critical for the normal development of the brain and retina, and in its absence there is evidence for abnormal migration of developing neurons in the brain. To understand this migration defect better, these investigators studied the effect of mutating this protein on the adhesion of cultured cells to protein-coated surfaces. Expression of the normal protein inhibited cell adhesion; however, when certain critical regions of the protein that control its membrane association were deleted, this effect was lost. These studies may have implications for how MARCKS is used to control migration of brain neurons during development.

Spizz G, and Blackshear PJ: Overexpression of the myristoylated alanine-rich c-kinase substrate inhibits cell adhesion to extracellular matrix components. Journal of Biological Chemistry (in press 2001).

Discovery of a New Cytochrome P450 Arachidonic Acid Hydroxylase in Brain. The cytochrome P450 enzyme system is highly responsive to environmental agents, generally breaking these agents down into smaller, more water-soluble components. These researchers cloned a new cytochrome P450 (CYP2J9), which is abundant in brain and highly expressed in the neuronal Purkinje cells involved with coordination and balance. The major product of this enzyme (19-HETE) inhibits triggers of neurotransmission which are also abundant in Purkinje cells. Importantly, the expression of this P450 is increased by mercury vapor which is a known neurotoxin. These data indicate that CYP2J9 is regulated by environmental factors and may play important functional roles in the brain.

Qu W, Bradbury A, Tsao CC, Maronpot R, Harry GJ, Davis L, Breyer MD, Waalkes M, Parker C, Falck JR, Chen J, Rosenberg R, and Zeldin DC: Cytochrome P450 CYP2J9, a New Mouse Arachidonic Acid ω -1 Hydroxylase Predominately Expressed in Brain. Journal of Biological Chemistry (in press 2001).

Imaging Blood-Brain Barrier Function. Capillaries in the brain constitute a barrier to the entry of foreign chemicals, such as neurotoxins and therapeutic drugs. This barrier, while vitally important to a living organism, makes it hard to study transport function in intact brain capillaries; there are few suitable in vitro techniques that both retain viability of the tissue and that allow the investigator to measure movement of molecules across the capillary endothelium (the innermost layer of the capillary vessel). This report introduces a new approach to studying excretory (central nervous system to blood) transport. These investigators used the optical sectioning capabilities of confocal microscopy to visualize and measure the accumulation of

fluorescent drugs within the internal spaces of freshly isolated capillaries from rat and pig brain. The images show that two export pumps constitute an active barrier to entry into the central nervous system.

Miller DS, Knobmann SN, Gutmann H, and Fricker G: Xenobiotic transport across isolated brain microvessels studied by confocal microscopy. Molecular Pharmacology 58: 1357-1367, 2000.

Regulation of Chondrocyte Development. During long bone development, chondrocytes (cartilage forming cells) located at the tip of the growing bone give rise to joint tissue, whereas the chondrocytes in the bone shaft undergo maturation and mineralization and are replaced by bone. While both populations of chondrocytes are critically important for skeletal development and skeletal function, it is not understood how chondrocytes follow these alternative pathways to distinct fates and functions. Researchers have recently identified a transcription factor (proteins that bind to DNA in a highly specific fashion and regulate the expression of groups of genes) that appears to play a role in the genesis of these populations of chondrocytes. Specifically, they have identified two structurally similar forms of a transcription factor from the developing skeleton. Expression of the A form stimulated chondrocyte maturation in culture, with deposition of a mineralized matrix, while expression of the B form maintained chondrocytes in a stable form and prevented the replacement of cartilage with bone. This study provides important information on molecular mechanisms by which articular chondrocytes persist through life and growth plate chondrocytes advance through maturation. It may also have significant medical implication for targets and means of therapeutic interventions in pathologies of skeletal development and function.

Iwamoto M, Higuchi Y, Koyama E, Enomoto-Iwamoto M, Kurisu K, Yeh H, Abrams WR, Rosenbloom J, and Pacifici M: Transcription factor ERG variants and functional diversification of chondrocytes during limb long bone development. Journal of Cell Biology 150: 27-40, 2000.

Decorin in Lyme Arthritis. *Borrelia burgdorferi* is the causative agent of Lyme disease. It is transmitted by infected ticks that deposit a small number of organisms in the skin of a host animal, leading to a localized infection. In Lyme disease, the mechanism of bacterial adhesion to host tissue may be important in determining both the fate of the initial changes in the skin and the ability of the organism to disseminate to other tissues. In order to disseminate, *B. burgdorferi* utilize a system of adhesion receptors expressed on their outer surface. The bacteria do not directly bind to collagen, but rather they bind to decorin, a proteoglycan (a type of molecule) in the extracellular matrix responsible for maintaining the underlying structure of connective tissue. Researchers recently created two mouse strains, identical in all respects except in their ability to produce decorin. When decorin-deficient mice were injected with *B. burgdorferi*, while the skin reactions were the same as those in decorin-normal mice, decorin-deficient animals showed lower numbers of bacteria invading the joint tissues and a lower incidence of arthritis. Decorin binding, therefore, is a major mechanism by which *B. burgdorferi* disseminates. This advance suggests that the local conditions in the joint tissue, for example the relatively large concentration of decorin in synovium (tissue that lines the joint) and cartilage, may create an environment conducive to the persistence of infection and local immune and inflammatory responses.

Brown EL, Wooten RM, Johnson BJ, Iozzo RV, Smith A, Dolan MC, Guol BP, Weis JJ, and Höök M: Resistance to Lyme disease in decorin-deficient mice. Journal of Clinical Investigation 107: 845-852, 2001.

Green Tea and Cancer Prevention. There is broad-based evidence that green tea or its constituent chemicals (the polyphenols) may protect against cancer of many types. The major polyphenol is termed epigallocatechin-3-gallate (EGCG). A number of studies have been undertaken to determine how this chemical and the green tea polyphenols in general act to inhibit the development of skin cancer, particularly following ultraviolet irradiation (the cause of most skin cancers seen in the U.S.). In a study looking at the basic functions of EGCG and at the effects of these polyphenols on UV induced skin changes, it was determined that topical application can decrease or prevent DNA damage from ultraviolet radiation when the chemicals are applied prior to ultraviolet radiation. In human skin, similar studies also demonstrated the inhibition of sunburn reactions following UV radiation and the reduction of the development of sunburn cells (microscopic cellular changes that indicate prior excess UV exposure) and damage to epidermal langerhans cells (immunologically active cells normally found in the skin which help protect against skin cancer development), all of which are indications of prevention of damage from ultraviolet radiation. These studies indicate the green tea polyphenols may have a variety of beneficial effects including topical application to human skin that will subsequently have ultraviolet exposure. Understanding the mechanisms of action of these products will assist in the development of potentially more effective and/or less toxic products that can be developed as pharmaceutical agents for both skin and systemic cancer prevention.

Ahmad N, Cheng P, and Mukhtar H: Cell cycle dysregulation by green tea polyphenol epigallocatechin-3-gallate. Biochemical and Biophysical Research Communications 275: 328-334, 2000.

Elmets CA, Singh D, Tubesing K, Matsui M, Katiyar S, and Mukhtar H: Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. Journal of the American Academy of Dermatology 44: 425-432, 2001.

Katiyar SK, Perez A, and Mukhtar H: Green tea polyphenol treatment to human skin prevents formation of ultraviolet light B-induced pyrimidine dimers in DNA. Clinical Cancer Research 6: 3864-3869, 2000.

Katiyar SK, Afaq F, Perez A, and Mukhtar H: Green tea polyphenol (-)-epigallocatechin-3-gallate treatment of human skin inhibits ultraviolet radiation-induced oxidative stress. Carcinogenesis 22: 287-294, 2001.

Molecular Genetic Basis of Sporadic Basal Cell Skin Cancer. Basal cell skin cancer is the most common cancer in the U.S. population. Most cases are sporadic and are the result of the lifelong accumulation of ultraviolet damage to the skin. There is a rare genetic form of the disease in which multiple basal cell carcinomas develop starting early in life. Several years ago, the genetic defect in the disease was determined to be caused by a defect in a gene called *patched* and abbreviated PTCH. Another protein and gene termed p53 has been associated with the development of various cancers including both basal cell and squamous cell (the other very common) skin cancer. Researchers have recently provided the first report of specific p53 mutations and the first report of the presence of UV specific mutations in both these genes in the same skin cancers. These studies demonstrate the importance of these two genes in the evolution of basal cell cancer. The PTCH gene was recognized and investigated because of its known association with the rare genetic form of the disease and the p53 gene because of its implication

in other cancers. In these studies, it is demonstrated that these genes either individually or together are important in sporadic basal cell cancers, whether of early or late onset, and that most of the mutations in these genes are due to UV damage. This further confirms the causative role of UV exposure in the development of this most common form of human cancer.

Ratner D, Peacocke M, Zhang H, Ping XL, and Tsou HC: UV-specific p53 and PTCH mutations in sporadic basal cell carcinoma of sun-exposed skin. Journal of the American Academy of Dermatology 44: 293-297, 2001.

Zhang H, Ping XL, Lee PK, Wu XL, Yao YJ, Zhang MJ, Silvers DN, Ratner D, Malhotra R, Peacocke M, and Tsou HC: Role of PTCH and p53 genes in early-onset basal cell carcinoma. American Journal of Pathology 158: 381-385, 2001.

New Biologic Markers Characterized for Scleroderma. Scleroderma is an autoimmune disorder that occurs more frequently in women than in men, usually between the ages of 45 and 55. The hallmark of scleroderma is widespread thickening of the skin, and can also include fibrosis or scarring of tissues in the lungs, heart, kidneys, intestinal tract, muscles and joints. Recent genetic studies in both an animal model and in a human population have implicated fibrillin-1 as important in understanding scleroderma. Fibrillin-1 is the major structural component (glycoprotein) of connective tissue microfibrils, which are important components of elastic fibers widely distributed throughout the body. In the first study, autoantibodies to fibrillin-1 were reported in sera of both the animal model for scleroderma and in patients with scleroderma, but not in patients with other connective tissue diseases such as lupus, rheumatoid arthritis, or Sjögren's syndrome. The level of antifibrillin-1 autoantibodies showed an ethnic variation, with concentrations being highest in scleroderma patients of Choctaw American Indians or Japanese background. The investigators speculated that this ethnic difference may be due to genetic variation in the immune response to fibrillin-1. In the second study, investigators went on to look at the specific antifibrillin autoantibodies in four ethnic groups: Choctaw, Japanese, African-Americans, and Caucasians. They found striking ethnic differences in the regions of fibrillin recognized by the antibodies. Caucasians were unique in showing a less than 50 percent incidence of antifibrillin autoantibodies. Unfortunately, in no ethnic group did the antifibrillin autoantibodies predict anything beyond the presence of scleroderma. The antifibrillin autoantibodies did not correlate with any major clinical features, other autoantibodies, or other genetic markers. Since fibrillin-1 is abnormally produced or processed in fibroblasts of scleroderma patients or animal models, the characterization of anti-fibrillin-1 autoantibodies in patients with scleroderma opens new lines of investigation to understand this disease.

Tan FK, Arnett FC, Reveille JD, Ahn C, Antohi S, Sasaki T, Nishioka K, and Bona CA: Autoantibodies to fibrillin 1 in systemic sclerosis: ethnic differences in antigen recognition and lack of correlation with specific clinical features or HLA alleles. Arthritis and Rheumatism 43: 2464-2471, 2000.

A New Pathway to Increased Bone Density in Mice. The structurally related group of proteins called "bone morphogenetic proteins," or BMPs, has been the subject of intense study. Most of the members of this protein family have the striking property of stimulating new bone formation if they are introduced into non-bone tissue such as muscle. BMPs may therefore be useful in rebuilding damaged bone and healing fractures. As more has been learned about BMPs,

however, it has become clear that they are not all the same. In particular, the family member called BMP3 has been puzzling. While samples of the protein purified biochemically from bone appeared to stimulate bone formation, the same protein made by genetic methods in the laboratory did not. In a series of experiments, investigators have now revealed that BMP3 has a function opposite to other BMPs: it inhibits bone formation, and that BMP3 normally functions to suppress net bone formation. Net loss of bone, leading to osteoporosis, occurs when bone resorption exceeds bone formation. The ability to induce net gain of bone mass, especially in trabecular regions, would make it possible to reverse bone loss and prevent fractures. While it still remains to be seen if BMP3 has the same effects in humans as in mice, it seems to offer a new approach to stimulating new bone formation. If a drug can be designed to block BMP3 interaction with its receptor, it would be expected to lead to an increase in bone density. The results so far with the mice lacking BMP3 suggest that there would be few serious side effects of such a drug.

Daluiski A, Engstrand T, Bahamonde ME, Gamer LW, Agius E, Stevenson SL, Cox K, Rosen V, and Lyons KM: Bone morphogenetic protein-3 is a negative regulator of bone density. Nature Genetics 27: 84-88, 2001.

Difficulty Extracting Social Information from Faces Characterizes Autism. Autism is a developmental neuropsychiatric disorder characterized by deficits in social behavior and communication, many of which may be attributable to difficulties understanding socially relevant cues, such as those available in facial expressions. The neural basis of this difficulty has been hypothesized to involve the amygdala, a limbic structure implicated in the perception of emotions such as fear. Patients with amygdalar damage have difficulty recognizing facial emotion and have difficulty making complex social judgements, such as trustworthiness, from faces. Behavioral tests sensitive to these deficits in patients with bilateral amygdala damage were used to examine eight high-functioning individuals with autism. They proved able to normally discriminate faces on the basis of identity and to accurately rate the intensity of emotional expression, thus ruling out a simple visuoperceptive basis for any deficits in processing facial emotion. Most, but not all, recognized basic emotions from facial expressions. Similar to patients with amygdalar damage, the autistic patients were unable to normally judge trustworthiness from faces. While preliminary, given the small sample size, these results suggest that some of the same processes impaired in individuals with known amygdalar damage may be dysfunctional in autism.

Adolphs R, Sears L, and Piven J: Abnormal processing of social information from faces in autism. Journal of Cognitive Neuroscience 13: 232-240, 2001.

Suppressing Unwanted Memories by Executive Control. Researchers are making significant progress in understanding “executive control” – that is, how people purposively direct their own mental processes and behavior. In one especially rigorous set of studies, new information has been obtained about peoples’ ability to suppress the conscious recollection of material previously stored in memory. Experimental participants (adults) were taught lists of word pairs, and then instructed to suppress memory of the second member of certain pairs when presented with the first member. Subsequently, participants were tested on all word pairs. Recall of the second members of those pairs for which participants had previously engaged in suppression was

significantly lower than recall on those pairs for which they had not engaged in suppression. Various experimental manipulations of stimuli, number of suppression trials, and participants' expectations and motivations produced converging evidence that memories of the second members of the pairs had indeed been suppressed, i.e., prevented from reaching conscious awareness, and that such suppression can become habitual and enduring. These results help elucidate the executive control mechanisms that underlie those phenomena often labeled by psychotherapists as repression or defense. However, contrary to some therapists' views, it appears that the learned suppression of conscious recollection is a commonplace occurrence, not limited to material associated with traumatic or disturbing experiences. Looking ahead, this research provides the basis for the development of new therapeutic techniques for uncovering suppressed memories and for constructing healthy new patterns of thought and behavior. [secondary – treatment]

Anderson MC, and Green C: Suppressing unwanted memories by executive control. Nature 410: 366-369, 2001.

ADHD in Girls. Previously, researchers found that boys with attention-deficit/hyperactivity disorder (ADHD) have significant differences in the sizes of certain areas of the brain compared to normal control subjects. Now researchers at NIH have examined the same brain areas in girls with ADHD to determine whether these areas are also different sizes in girls. They found that certain areas of the cerebellum, a region of the brain involved in movements, are significantly smaller in these girls, similar to prior findings in ADHD boys. However, none of the other regions of the brain identified in ADHD boys were altered in ADHD girls. This study will help to understand the pathophysiology of ADHD, including any gender differences.

Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T, Vaituzis AC, Blumenthal JD, Nelson J, Bastain TM, Zijdenbos A, Evans AC, and Rapoport JL: Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. Archives of General Psychiatry 58: 289-295, 2001.

Making Employers Care about Mental Disorder Related Disability: The Problem of “Presenteeism.” Recently, employers have found the issue of “presenteeism” – when an employee goes to work ill and therefore functions at a diminished capacity – to be of increasing concern. Because of the associated stigma with mental disorders such as depression, these illnesses exact a particularly high toll on workplace productivity. Analyzing data from a longitudinal survey of more than 6,000 employees from three corporations in 1993 and 1995, researchers examined the link between depression, health care satisfaction, and work outcome. The study revealed that those with depression were twice as likely to miss work in both years as those without depressive symptoms in either year. In addition, depressed employees had seven times the rate of decreased work effectiveness or presenteeism. Furthermore, responses from depressed employees suggested a possible association between problems in clinical care and worse 2-year outcomes. This research addresses the work-related costs of depression, and the importance of treating depression in terms of its potential impact on work productivity.

Druss BG, Schlesinger M, and Allen H: Depressive symptoms, satisfaction with health care, and 2-year work outcomes in an employed population. American Journal of Psychiatry 158: 731-734, 2001.

Molecules Mediating Synaptic Maturation Identified. Although synapses have been studied extensively, the mechanisms underlying their formation and maturation remain poorly understood. Two independent studies now demonstrate that the synaptic scaffolding protein PSD-95 and a class of cell adhesion molecules known as the integrins play key roles in synaptic maturation. In the first study, chronic overexpression of PSD-95 in developing neurons accelerated synapse maturation both pre- and postsynaptically. Presynaptically, larger numbers of synaptic vesicles were detected, as were higher levels of proteins involved in synaptic vesicle release such as synaptophysin and synaptic vesicle protein 2 (SV2). On the postsynaptic side, increases in the accumulation of glutamate receptors at synapses as well as increases in the number and size of dendritic spines were also found when PSD-95 levels were elevated. In the second study, chronic blockade of the integrin binding site and antibodies against integrins were used to show that the integrins mediate the developmental maturation of synaptic activity parameters. Together these studies identify two of the key molecules that participate in the synaptic maturation process.

El-Husseini AED, Schnell E, Chetkovich DM, Nicoll RA, and Brecht DS: PSD-95 involvement in maturation of excitatory synapses. Nature 290: 1364-1368, 2000.

Chavis P, and Westbrook G: Integrins mediate functional pre- and postsynaptic maturation at a hippocampal synapse. Nature 411: 317-321, 2001.

Cortical Plasticity Following Visual Experience. The adult brain is able to continuously change its activity in response to new experiences. Researchers at NIH are working to learn how the brain detects novelty versus recognizing a familiar visual scene. They found that in adult monkeys neurons near one another in the inferior temporal cortex, a region involved in very high level visual processing, would begin to respond in concert to familiar stimuli. This concert was restricted to neurons close to one another, within a half millimeter or so. The researchers concluded that the neurons were organizing themselves into clusters that responded in the same way to various stimuli. This clustering may underlie the formation of memories in this visual part of the brain.

Erickson CA, Jagadeesh B, and Desimone R: Clustering of perirhinal neurons with similar properties following visual experience in adult monkeys. Nature Neuroscience 3: 1143-1148, 2000.

Turning Perception into Action. The prefrontal cortex is the region of the human brain that integrates information from the senses, along with memories of past experiences, and translates these into action. Using a very simple model of this behavior, researchers at NIH have investigated this process in non-human primates. They created an optical illusion in which monkeys perceived that a spot had moved in one direction, when in fact it had moved in the opposite direction, but the background had moved as well. The researchers knew what the monkey perceived because the monkey turned its gaze in the direction of the perceived motion. The investigators recorded from individual neurons in the prefrontal cortex and found a large population that responded to the monkey's perception of the direction in which the spot had moved. The findings indicate that the prefrontal cortex is integrating motion information as well as perceptual reports. Understanding the normal functions of prefrontal cortex – and, especially,

its role in interpreting representations of physical stimuli – will help in understanding the brain processes that guide behavior, which are disturbed in both schizophrenia and mood disorders.

Lebedev MA, Douglass DK, Moody SL, and Wise SP: Prefrontal cortex neurons reflecting reports of a visual illusion. Journal of Neurophysiology 85: 1395-1411, 2001.

Overcoming Barriers to Access of Antiviral Therapy in Racial and Ethnic Minorities

Infected with HIV. African-Americans with AIDS continue to lag behind non-minority groups in the use of antiretroviral regimens. To understand reasons for this lag, NIH-funded researchers compared rates of treatment of newer antiviral treatments across sociodemographic groups during the 3 years following the introduction of these treatments and examined patterns of use of these therapies over time. The study was based on adult Medicaid participants who were diagnosed with AIDS in New Jersey from 1991-1998. Surveillance and claims data were used to examine use of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) – combination therapies that include new, more effective antiviral drugs – among New Jersey Medicaid beneficiaries with AIDS. In 1996, there were sharp disparities in use of PI/NNRTI therapy among racial minorities and injection drug users, even after controlling for other patient characteristics. By 1998 these gaps were reduced. Participation in a statewide Medicaid waiver program, which was implemented to improve access to and coordination of home and community-based care for persons with HIV/AIDS, has been associated with a narrowing of racial differences in the use of these new drugs as new treatments become standard care. These results suggest the need to address non-financial barriers to access for these therapies that are specific to traditionally disadvantaged populations.

Sambamoorthi U, Moynihan PJ, McSpiritt E, and Crystal S: Use and diffusion of protease inhibitors and non-nucleoside reverse transcriptase inhibitors among Medicaid beneficiaries with AIDS. American Journal of Public Health (in press 2001).

Visual Discrimination Learning Requires Sleep After Training. Normally, performance on a visual discrimination task improves with practice. This improvement is thought to involve skill learning and a form of memory called procedural memory. The improvement of the memory is thought to be due to a consolidation process that continues for some time after the training and which can be enhanced or reversed by various manipulations. Research has shown that the improvement occurs in proportion to the amount of deep sleep in the first part of the night and active sleep in the last quarter of the night. Further, performance following a single training session improves after 24 hours and shows greater improvement after a second night of sleep. However, no improvement was seen when testing occurred on the same day as training, and one night of sleep deprivation blocked the improvement in performance even after two full nights of recovery sleep. These findings suggest that the consolidation of this skill learning is a process that continues over at least 2 days, but even normal sleep on the second night cannot replace the lost effects of the first night of deprivation. Thus, the consolidation of the visual discrimination task involves initial training with full attention and awareness, and it continues in the absence of conscious attention during sleep.

Stickgold R, James L, and Hobson JA: Visual discrimination learning requires sleep after training. Nature Neuroscience 3: 1237-1238, 2000.

Recognition Memory. New experiences continuously modify the brain. Using functional magnetic resonance imaging, researchers at NIH have shown that the cortex undergoes rapid and long lasting changes in neural activity after subjects viewed a nonsense object (objects that do not have pre-existing representations in memory) one time. In visual areas, these changes occurred very rapidly, while in memory-related areas, the changes were not seen until longer after the stimulus. Both remained when the patients were studied three days later, indicating that these changes are long-lasting. This study provides new insights into memory mechanisms and the location of parts of different memory systems.

van Turennout M, Ellmore T, and Martin A: Long-lasting cortical plasticity in the object naming system. Nature Neuroscience 3: 1329-1334, 2000.

How the Brain Encodes Abstract Rules. The ability to learn abstract rules that transcend a specific experience and apply them to similar situations is a hallmark of intelligent behavior. But how the brain manages to develop a general response (e.g., 'rules' for restaurant dining) from single experiences remains poorly understood. Observations of people with brain damage suggest that a part of the cerebral cortex called the prefrontal cortex is critical to this ability. Now, studies recording electrical responses of single nerve cells in the brains of monkeys have identified cells in the prefrontal cortex that can encode abstract rules. Such studies are helping to reveal the neurological foundations of human cognition that will serve as a basis for understanding how higher brain processes are compromised by trauma and disease.

Wallis JD, Anderson KC, and Miller EK: Single neurons in prefrontal cortex encode abstract rules. Nature 411: 953-956, 2001.

A Role for Endogenous Cannabinoids in the Brain. Marijuana affects the brain by interacting with a nerve cell protein called the cannabinoid receptor. Cells have the receptor, or sensor, because the brain produces substances similar to marijuana, called endogenous cannabinoids. Until recently scientists have been at a loss to explain the functions of these chemical signals in the brain. Two studies have now reported that the endogenous cannabinoids carry signals backward in the brain, conveying information in the reverse of the usual flow of signaling across synapses. The process fine-tunes future signals sent by neighboring nerve cells, leading to accurate memory-formation and motor coordination, among other functions. The new research suggests marijuana use most likely overwhelms the system with a powerful *exogenous* cannabinoid that interferes with these normal endogenous cannabinoid signaling processes.

Wilson RI, and Nicoll RA: Endogenous cannabinoids mediate retrograde signaling at hippocampal synapses. Nature 410: 588-592, 2001.

Kreitzer AC, and Regehr WG: Retrograde inhibition of pre-synaptic calcium influx by endogenous cannabinoids at excitatory synapses onto Purkinje cells. Neuron 29: 717-727, 2001.

Transgenic Rat Model of the AIDS Virus. For the first time scientists have engineered a rat to contain the genome of the HIV-1 virus which causes AIDS. The rats exhibit many of the signs

that affect people with AIDS, including wasting, skin lesions, eye problems, respiratory difficulties, and neurological signs. The rats may be a valuable model for understanding how the HIV virus causes the chronic problems of AIDS and for testing therapies targeted to stages of the virus after its integration into the host genome.

[secondary – treatment]

Reid W, Sadowska M, Denaro F, Rao S, Foulke JJr, Hayes N, Jones O, Doodnauth D, Davis H, Still A, O'Driscoll P, Huso D, Fouts T, Lewis G, Hill M, Kamin-Lewis R, Wei C, Ray P, Gallo RC, Reitz M, and Bryant J: An HIV-1 transgenic rat that develops HIV-related pathology and immunological dysfunction. Proceedings of the National Academy of Sciences USA 98: 9271-9276, 2001.

Familial Dysautonomia Gene Discovery. Familial dysautonomia, also known as Riley-Day syndrome or hereditary sensory and autonomic neuropathy type III, is an invariably fatal, inherited disorder that affects sensory nerve cells and the autonomic nervous system. The wide range of symptoms reflects dysfunction of sensory, gastrointestinal, respiratory, and cardiovascular systems normally regulated by these nerve cells. Two independent teams of scientists have determined that the disease is caused by defects in a gene *IKBKAP*, which normally regulates the activity of other genes. The findings immediately provide the basis for carrier screening in the Ashkenazi Jewish population, where the mutation is most common, and in the long run will lead to better understanding of the disorder. In particular, if scientists can determine why, as the studies showed, some types of cells, but not nerve cells, can make a functional *IKBKAP* protein despite the mutation, they may be able to suggest strategies for treatment. [secondary – diagnosis]

Slaughenhaupt SA, Blumenfeld A, Gill SP, Leyne M, Mull J, Cuajungco MP, Liebert CB, Chadwick B, Idelson M, Reznik L, Robbins CM, Makalowska I, Brownstein MJ, Krappmann D, Scheidereit C, Maayan C, Axelrod FB, and Gusella JF: Tissue-specific expression of a splicing mutation in *IKBKAP* gene causes familial dysautonomia. American Journal of Human Genetics 68: 598-605, 2001.

Anderson SL, Coli R, Daly IW, Kichula EA, Rork MJ, Volpi SA, Ekstein J, and Rubin BY: Familial dysautonomia is caused by mutations of the *IKAP* gene. American Journal of Human Genetics 68: 753-758, 2001.

Flies and Brain Disorders. The fruitfly, *Drosophila*, has long been a favorite for scientists investigating fundamental biological processes because of its many advantages as an experimental subject. With recent progress in unraveling the human and fly genomes, the remarkable similarities between basic biological processes in flies and humans have become even more apparent. In the last few years, researchers have begun to use the versatile fly to explore aspects of neurological disorders that are much harder to explore in more complex animals, including how multiple genes interact and the steps in complex biochemical pathways that lead to disease. This year, flies with a mutation in the protein *tau*, which is implicated in Alzheimer's disease, exhibited key features of the human disorder, including an adult onset, progressive loss of brain cells and early death. Similarly flies with defects in genes that cause hereditary ataxias, neurofibromatosis, lissencephaly and Parkinson's are helping to unravel the underpinnings of those diseases.

Wittman CW, Wszolek MF, Shulman, JM, Salvaterra PM, Lewis J, Hutton M, and Feany MB: Tauopathy in *Drosophila*: neurodegeneration without neurofibrillary tangles. Science 293: 711-714, 2001.

Glia Regulate Synapses. Glial cells outnumber nerve cells in the human brain by ten to one. Although for many years glia were regarded as passive supporting cells, evidence is accumulating that glia release chemicals crucial for the growth and survival of nerve cells, regulate the concentration of signaling molecules in the fluid that surrounds brain cells, guide growing nerve fibers, and react as a first line of defense against disease and trauma. Now, scientists have found in cell culture that glial cells also are involved with the most fundamental information processing abilities of the brain by regulating the number of synapses that form between nerve cells and by maintaining healthy synaptic connections. Synapses are the functional contacts between nerve cells and the site of changes during learning. Fostering new synapses will be essential for rebuilding the brain and spinal cord following stroke, trauma, and disease. In addition, maintaining synapses is crucial for the healthy function of the brain, so these results have many potential implications.[secondary – treatment]

Ullian EM, Sapperstein SK, Christopherson KS, and Barres BA: Control of synapse number by glia. Science 291: 657-660, 2001.

Glial Cells may be Culprits in Neuropathic Pain. Pain is a normal and necessary sensation, but many people suffer from neuropathic pain states in which pain persists abnormally, spreads to non-injured tissue, and even gentle touch can cause excruciating pain. Considerable evidence has now accumulated that glia, the supporting cells of the brain and spinal cord, may contribute to persistent pain states. In one recent finding, for example, spinal cord glia respond to contact with the gp120 protein from the HIV virus by releasing several inflammation-promoting chemicals usually associated with immune cells. This may contribute to the painful neuropathy that often accompanies AIDS. In the future, drugs that target glial cells and the substances they release may provide a novel strategy for treatment of many persistent pain states. [secondary – treatment]

Watkins LR, Miligan ED, and Maier SF: Glial activation: a driving force for pathological pain. Trends in Neuroscience 24: 450-455, 2001.

Milligan ED, O'Connor KA, Nguyen KT, Armstrong CB, Twining C, Gaykema RPA, Holguin A, Martin D, Maier SF, and Watkins LR: Intrathecal HIV-1 envelope glycoprotein gp120 induces enhanced pain states by spinal cord proinflammatory cytokines. Journal of Neuroscience 21: 2808-2819, 2001.

Visualizing Migraine Auras. A migraine is a severe headache with stabbing or pulsing pain, often associated with nausea, vomiting, and sensitivity to light, sound or movement. In about 20 percent of cases, a migraine is preceded by a visual aura, an illusion of an expanding crescent of shining or scintillating shapes followed by a blind spot and later headache. Now, researchers have imaged the brain during the onset and progression of visual auras using functional MRI. Changes in brain activity in visual areas of the cerebral cortex corresponded to the perceived position of the shapes. The progression of the aura also corresponded to a phenomenon known as cortical spreading depression that was previously studied in animals and suspected to contribute to migraine. A better understanding of migraine will ultimately lead to better therapy and prevention.

Hadjikhani N, Sanchez del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RBH, Sorenson AG, and Moskowitz MA: Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proceedings of the National Academy of Sciences USA 98: 4687-4692, 2001.

Pain Perception. Pain is a significant medical problem. It is the most common reason for seeking medical treatment and causes tremendous loss of work productivity and quality of life. New research shows that a single component of a glutamate receptor (a cell-surface protein complex that binds to the amino acid neurotransmitter, glutamate, and transmits a signal to the neuron) might influence the perception of chronic pain. This finding suggests that developing drugs to target this component of the glutamate receptor may produce more effective therapies for persistent pain. [secondary – treatment]

Wei, F, Wang GD, Kerchner GA, Kim SJ, Xu HM, Chen ZF, and Zhou M: Genetic enhancement of inflammatory pain by forebrain NR2B overexpression. Nature Neuroscience 4: 164-169, 2001.

New Insights into Neurotransmitter Release. Neurotransmitters (the chemical messengers between nerve cells) are packaged into small vesicles that attach to the cell membrane and await the signal for release. The interactions between proteins on the vesicle and on the membrane are often compared to firing a gun; some proteins “prime” the vesicle and others “trigger” release. Now, a new study has demonstrated that UNC-13, a protein found in all animals examined so far, “cocks” the vesicle prior to the release trigger. Neurotransmitter release is the basis of all activity in the brain, thus a better understanding of the process should be applicable to conditions in which neurotransmitter release is impaired, including exposure to toxins or drugs of abuse.

Richmond JE, Weimer RM, and Jorgensen EM: An open form of syntaxin bypasses the requirement for UNC-13 in vesicle priming. Nature 412: 338-341, 2001.

New Model System for the Study of West Nile Virus Encephalitis. West Nile Virus (WNV) has emerged in recent years in North America, presenting a threat to public health. The most serious manifestation of WNV in humans is fatal encephalitis (inflammation of the brain). NIH-supported researchers have developed a hamster model of WNV encephalitis in which infected animals show signs of encephalitis 6 days after infection, and about 50-70 percent of the animals succumb to infection. This animal model will provide an inexpensive, readily available means to study pathogenesis and test diagnostics, vaccines, and therapies.

Xiao SY, Guzman H, Zhang H, Travassos da Ros APA, and Tesh RB: West Nile virus infection in the golden hamster (*Mesocricetus auratus*): a model of West Nile encephalitis. Emerging Infectious Diseases 7: 714-721, 2001.

Gene Abnormality for Cystic Fibrosis May Be Responsible for Development of Chronic Sinusitis. Gene alterations known to cause the inherited disorder cystic fibrosis (CF), characterized by mucous membrane abnormalities in the lungs, appear also to contribute to chronic sinus problems in some people. CF occurs only when individuals inherit two mutant copies of the cystic fibrosis transmembrane regulator (CFTR) gene, one from each parent. An NIH-supported investigator and colleagues discovered that individuals who inherit only a single

copy of a mutant CFTR gene are highly predisposed to develop chronic sinusitis. Mutations in the CFTR gene may account for about 1 in 15 cases of chronic sinusitis. Future research efforts that focus on CFTR gene alterations may prove critical for the development of new prevention strategies and more effective treatments for chronic sinusitis.

Wang X, Moylan B, Leopold DA, Kim J, Rubenstein RC, Togias A, Proud D, Zeitlin PL, and Cutting GR: Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. The Journal of the American Medical Association 284: 1814-1819, 2000.

Inherited Mutation Linked to Increased Incidence of Lymphoma. ‘Fas’ is a receptor on the surface of immune cells that transmits a signal for the cell to self-destruct through a process termed programmed cell death (PCD). PCD maintains equilibrium of the immune cell population. Certain mutations in Fas that prevent PCD result in a disease called autoimmune lymphoproliferative syndrome (ALPS). Recently, NIH scientists determined that inherited Fas mutations associated with ALPS increase the lifetime risk of developing lymphoma (cancer of the white blood cells). This determination identifies a new class of gene associated with cancer risk. Importantly, it also provides information on cancer predisposition for individuals with ALPS.

Straus SE, Jaffe ES, Puck JM, Dale JK, Elkon KB, Rösen-Wolff A, Peters AMJ, Sneller MC, Hallahan CW, Wang J, Fischer RE, Jackson CM, Lin AY, Bäuml C, Siegert E, Marx A, Vaishnav AK, Grodzicky T, Fleisher TA, and Lenardo MJ: The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. Blood 98: 194-200, 2001.

Exposure to High Levels of Cat Allergen Results in Protective Immune Response.

Exposure to many indoor allergens, such as house dust mites, may lead to allergic sensitization, a process whereby the body is primed to mount a strong immune response upon reexposure to an allergen. Such sensitization increases the risk of developing allergies and asthma.

Paradoxically, NIH-supported scientists have discovered that high levels of cat allergen in the home decrease the risk of sensitization, apparently because of the particular way the immune system responds to cat allergen. They found that high levels of cat allergen prompted children’s immune systems to make IgG, a class of antibody that does not cause an allergic response, as opposed to allergy-inducing IgE antibodies. Elucidating the factors that regulate IgG and IgE production may aid in the development of new prevention strategies and more effective allergy and asthma treatments.

Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, and Sporik R: Sensitization, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 357: 752-756, 2001.

Identification of an Induced Cell Surface Channel on Red Blood Cells Infected with Malaria Parasites. Malaria is responsible for more than 1 million deaths worldwide each year. The disease is caused by plasmodium parasites that are transmitted by a group of mosquitoes in the genus *Anopheles*. The life cycle of the malaria parasite is complex and includes reproduction initially in the infected person’s liver cells and then, repeatedly, in red blood cells (RBCs). Scientists have known for more than two decades that the growth of the malaria parasite in RBCs

is accompanied by increased uptake of nutrients by these cells. However, neither the mechanism of uptake nor the exact role of the malaria parasite in this process had been elucidated. Recently, NIH scientists, using a method for determining electrical conductance within a cell, termed “whole-cell voltage clamping,” found that malaria parasites induce the opening of a new channel through the surface of the RBC, which potentially serves a role in parasite nutrient acquisition. This advance provides a potential target for vaccine or drug development against malaria.

Desai SA, Bezrukov SM, and Zimmerberg J: A voltage-dependent channel involved in nutrient uptake by red blood cells infected with the malaria parasite. Nature 406: 1001-1005, 2000.

HIV Can Bind Efficiently to Immune Cells that Lack CD4, the Primary HIV Receptor Molecule. CD4 is a molecule present on the surface of one subset of immune cells called “helper T cells” that serves as a receptor for human immunodeficiency virus (HIV). During the course of HIV infection, the virus uses the CD4 molecule to enter in and destroy these critical immune cells, rendering the individual’s immune system incapable of defending against other infections. Recently, NIH scientists showed that HIV also is capable of binding to different subsets of immune cells that lack the CD4 surface molecule. This demonstrates that the binding of HIV to immune system cells can occur independent of CD4. Although HIV bound to these cells did not infect them, it did circulate throughout the body avoiding destruction by the immune system. Moreover, the investigators found that HIV attached to these cells is considerably more efficient at infecting helper T cells than free-circulating virus. This suggests that the binding of HIV to cells lacking the CD4 molecule represents a potentially significant mechanism for persistence of the virus.

Olinger GG, Saifuddin M, and Spear GT: CD-4 negative cells bind human immunodeficiency virus type 1 and efficiently transfer virus to T cells. Journal of Virology 74: 8550-8557, 2000.

Determination of Differences in Cytotoxic T-Lymphocyte Responses in Early and Chronic HIV Infection. Cytotoxic T lymphocytes (CTLs), or “killer T cells,” are immune system cells that play a critical role in controlling human immunodeficiency virus (HIV) infection by specifically eliminating HIV-infected cells. Thus, the initial induction and subsequent maintenance of CTL function has remained an important goal of preventative and therapeutic strategies for HIV/AIDS. NIH investigators recently demonstrated that the CTL responses that predominate in the acute (early) phase of infection are distinctly different from those that predominate during the chronic (later) stages of HIV infection. This finding is important because previous research efforts have focused on CTL from chronically infected people, which may not be the most relevant to controlling disease. This advance adds to the body of knowledge on HIV/AIDS and is a potentially important consideration in HIV vaccine design.

Goulder PJR, Altfeld MA, Rosenberg ES, Nguyen T, Tang Y, Eldridge RL, Addo MM, He S, Muckerjee JS, Phillips MN, Bunce M, Kalams SA, Sekaly RP, Walker BD, and Brander C: Substantial differences in specificity of HIV-specific cytotoxic T cells in acute and chronic HIV infection. Journal of Experimental Medicine 193: 181-193, 2001.

Viral Fusion: New Clues on Influenza Entry into Cells. Influenza enters and infects cells by a mechanism that involves the fusion of viral and host cell membranes. A peptide (protein

fragment) on the surface of the virus facilitates the fusion process. NIH-supported researchers developed a system to determine the detailed structure of an influenza fusion peptide using an artificial membrane. Changes in pH induce fusion peptides to bend and penetrate deeply into the host cell membrane, thereby facilitating mixing of the virus and host cell membrane lipids and release of the viral genome into the host cell. Understanding the viral fusion process will allow researchers to more specifically target new antiviral therapies for influenza and other viruses that use membrane fusion as their means of infecting cells.

Han X, Bushweller JH, and Cafiso DS, and Tamm LK: Membrane structure and fusion-triggering conformational change of the fusion domain from influenza hemagglutinin. Nature Structural Biology 8: 715-720, 2001.

Regulatory Pathway Identified that Controls Resistance to the Beta-Lactamase Class of Drugs in *Staphylococcus aureus*. Successful implementation of antibacterial therapy has become increasingly difficult because of widespread antimicrobial resistance. NIH-supported researchers identified a regulatory pathway that controls resistance to Beta-lactamase antibiotics (antibiotics structurally related to penicillin) in *Staphylococcus aureus*. Specifically, they discovered that, in the presence of the antibiotic, resistance is modulated in a multi-step pathway involving at least two proteins, a “DNA-binding repressor protein” and a “sensor-transducer protein” that interact to turn on and off genes and cause other proteins to be made. Understanding the fundamental processes involved in antimicrobial resistance within microbes forms an important basis for the development of prevention and treatment interventions.

Zhang HZ, Hackbarth CJ, Chansky KM, and Chambers HF: A proteolytic transmembrane signaling pathway and resistance to β -lactams in staphylococci. Science 291: 1962-1965, 2001.

Controlling Inflammation by a Synthetic Molecule that Targets the Heart of the Process. In autoimmune diseases such as rheumatoid arthritis, chronic inflammation causes serious injury to many tissues and organs. One of the key cellular molecules that controls inflammation within cells of the immune system is a molecule known as nuclear factor kappa B (NF- κ B). An NIH-supported investigator and others analyzed the molecular structure of regulatory molecules that affect the activation of NF- κ B, and designed a synthetic molecule to inhibit its activation. The synthetic molecule prevented inflammation in two mouse models of inflammatory disease. These findings may aid in the development of new therapeutic approaches for the treatment of autoimmune diseases and other inflammatory diseases.

May MJ, D’Acquisto F, Madge LA, Glöckner J, Pober JS, and Ghosh, S: Selective inhibition of NF- κ B activation by a peptide that blocks the interaction of NEMO with the I κ B kinase complex. Science 289: 1550-1554, 2000.

A Molecule Discovered on Immune Cells Plays a Central Role in Generating Antibodies. T cells are immune system cells involved in the coordination of the immune response. One function of T cells is to direct other immune cells, called B cells, to make different classes of antibodies. The class of antibody produced is determined in part by the T cell that interacts with the antibody-producing B cell. This fate decision is mediated by a T-cell surface protein called ICOS (inducible co-stimulatory molecule) that binds to a molecule on the B cell called B7RP-1. Now, NIH-funded scientists have demonstrated, in mice lacking a functional ICOS protein, that ICOS is critical for the production of the full range of classes of antibody that mice normally

produce. This finding shows the ICOS:B7RP-1 pathway to be a potential target for interventions to enhance vaccine efficacy and to inhibit allergic or inflammatory diseases.

McAdam AJ, Greenwald RJ, Levin MA, Chernova T, Malenkovich N, Ling V, Freeman GJ, and Sharpe AH: ICOS is critical for CD40-mediated antibody class switching. Nature 409: 102-105, 2001.

Intravenous Immunoglobulin Prevents Inflammation through an Inhibitory Receptor Molecule. Intravenous immunoglobulin (IVIG), a product containing antibodies harvested from human blood, has well recognized anti-inflammatory properties. However, it was not clear how IVIG elicits these effects. Recently, an NIH-supported investigator and colleagues determined that the anti-inflammatory properties of IVIG are mediated through an inhibitory pathway triggered by an antibody-binding receptor called Fc gamma receptor IIB (FcRIIB). These receptors, located on the surface of macrophages (specialized immune cells that engulf and destroy antibody-coated cells), bind the antibodies in IVIG. As a result, protection is provided against inflammation. Manipulation of this inhibitory receptor pathway may lead to the development of new treatments for immune-mediated diseases, including some autoimmune disorders.

Samuelsson A, Towers TL, and Ravetch JV: Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 291: 484-486, 2001.

Initiation of Smoking: Genes Play an Important Role. The development of a smoking habit involves many phases including initiation of smoking and the development of nicotine dependence. Research suggests that genetic factors may play a key role in smoking initiation and the progression to nicotine addiction. One candidate gene is the tryptophan hydroxylase (TPH) gene. The TPH gene is critical to the biosynthesis of serotonin, a neurotransmitter whose function is often altered in addiction. Thus, researchers investigated two TPH gene markers in a large population-based study to determine if there is an association between the gene and initiation of smoking or progression to nicotine dependence. The study looked at three groups, those who had never smoked, those who were regular smokers but had low scores on a test for dependence, and regular smokers with high dependence scores. In comparing lifetime nonsmokers with regular smokers, scientists found significantly different allele, genotype, and haplotype frequencies in the TPH gene markers, suggesting an association between smoking initiation and the gene. But no significant differences in the TPH gene markers were seen when comparing the two groups of regular smokers. Thus, the gene may not be associated with progression to nicotine addiction.

Sullivan PF, Jiang Y, Neale MC, Kendler KS, and Straub RE: Association of the tryptophan hydroxylase gene with smoking initiation but not progression to nicotine dependence. American Journal of Medical Genetics 105: 479-484, 2001.

Potential New Target for the Treatment of HIV. Successful retroviral infection requires the integration of the viral genome into the host cell DNA. Using genetic knockout technology to delete the enzyme poly(ADP-ribose) polymerase-1 (PARP-1) scientists have discovered that HIV-1 infection can be prevented in mice lacking this nuclear enzyme. Because PARP-1 appears to mediate the integration of the viral genome into the host genome, medications that inhibit this enzyme may be effective in the treatment of HIV. [secondary – treatment]

Ha HC, Juluri K, Zhou Y, Leung S, Hermankova M, and Snyder SH: Poly(ADP-ribose) polymerase-1 is required for efficient HIV-1 integration. Proceedings of the National Academy of Sciences USA 98: 3364-3368, 2001.

Prenatal Exposure to Methamphetamine Increases Neurotoxic Risk for Male Offspring.

Methamphetamine use by females of child-bearing age is a major public health concern in terms of the long-term risk to the exposed fetus. Studies using mice indicate that male offspring exposed to methamphetamine during 7 to 18 days of gestation were more susceptible to the neurotoxic effects of methamphetamine when exposed in adulthood. This was indicated by greater methamphetamine-induced reductions of dopamine in several brain regions. These findings raise the concern that male methamphetamine abusers may be at risk for an enhanced neurotoxic risk if they were exposed to the drug in utero.

Heller A, Bubula N, Lew R, Heller B, and Won L: Gender-dependent enhanced adult neurotoxic response to methamphetamine following fetal exposure to the drug. Journal of Pharmacology and Experimental Therapeutics 298: 769-779, 2001.

Morphine Can Alter Immune System Function: The Role of Substance P. Substance P (SP) is a neuropeptide that communicates between the central nervous system and the immune system, modulating immune and inflammatory responses. Opiates, such as morphine, also modulate the function of the immune system, and now research shows that there is an important connection between morphine and SP. Researchers investigating the effects of morphine on the production of SP and its receptor found that morphine increases the production of SP and its receptor in key human immune cells – mononuclear phagocytes and lymphocytes. Since SP regulates inflammation of the central nervous system and other immunologic events, these results suggest that morphine-induced SP expression in immune system cells may be of importance in the development of immune system related diseases, such as AIDS.

Li Y, Tian S, Douglas SD, and Ho WZ: Morphine up-regulates expression of substance P and its receptor in human blood mononuclear phagocytes and lymphocytes. Cellular Immunology 205: 120-127, 2000.

Hepatitis C Risk is not Limited to Those Who Inject. Hepatitis C virus (HCV) infection is a major health problem in the U.S. An estimated 4 million Americans – about 2 percent of the population – are infected and an average of 30,000 new infections occur annually. Sixty percent of all new cases of acute HCV infection are attributed to syringe and needle-sharing, thus prevalence of HCV is particularly high among injecting drug users. But researchers conducting a study of the prevalence of HCV infection among New York City drug users found a higher than expected HCV infection rate among non-injecting drug users. Of 107 women and 251 men from the Lower East Side of Manhattan who reported never injecting, 14 percent of the women

and 18 percent of the men were found to be infected with HCV. Of 171 women in East Harlem who reported no history of injection drug use, 17 percent were found to be infected. Although these rates were lower than for those with a history of injection drug use (from 54 to 61 percent), they were higher than the general population. The findings may indicate that use of needles and syringes is not the only drug-related risk factor for HCV infection. Thus, research into other routes of HCV transmission among non-injecting drug-users is needed.

Tortu S, Neaigus A, McMahon J, and Hagen D: Hepatitis C among non-injecting drug users: a report. Substance Use & Misuse 36: 523-534, 2001.

Researchers Develop Antibodies that Recognize Hepatitis C Virus. One of the critical problems in controlling hepatitis C virus (HCV) infection is the variability of the virus with more than nine distinct types of virus known. A further complication is the added variability of HCV envelope proteins, E1 and E2. These proteins, especially E2, enable the virus to bind to human immune cells leading to the spread of the disease within the body. In an effort to characterize the HCV envelope proteins and look for ways to prevent binding of the virus to immune cells, particularly T cells, researchers developed several HCV-specific, monoclonal antibodies from a person infected with HCV. The researchers found that not only did several of the antibodies recognize a variety of E2 formations, but several also prevented the binding of E2 to T cells that display a receptor called CD81. The demonstration of broadly effective antibodies in an individual with apparently controlled HCV infection suggests the usefulness of the strategy in characterizing and then producing antibodies that may be useful as therapy for the disease. [secondary – treatment]

Hadlock KG, Lanford RE, Perkins S, Rowe J, Yang Q, Levy S, Pileri P, Abrignani S, and Fong SKH: Human monoclonal antibodies that inhibit binding of hepatitis C virus E2 protein to CD81 and recognize conserved conformational epitopes. Journal of Virology 74: 10407-10416, 2000.

Experimental Animal Model Reveals Ability of Soy to Reduce Pain. Aspirin and morphine, as well as other pharmaceuticals, are well-characterized pain reducing agents. That property has also been attributed to certain complementary and alternative therapies, such as acupuncture or meditation. Diet, however, has not been associated with such activity. Recently investigators showed that rats fed a high soy diet *prior* to a nerve-injuring procedure experienced less pain following the procedure than cohorts fed with a no-soy diet. While pain reduction could not be demonstrated in rats fed a high-soy diet *following* the nerve-injuring event, the study merits follow-up to explore more fully the connection between diet and pain sensation and the attendant opportunities for therapeutic advantage.

Shir Y, Raja SN, Weissman CS, Campbell JN, and Seltzer Z: Consumption of soy diet to nerve injury preempts the development of neuropathic pain in rats. Anesthesiology (in press 2001).

Treatment for Persistent Asthma. The currently recommended therapy for persistent asthma involves administration of both an inhaled drug known as a corticosteroid (such as triamcinolone), which acts to reduce inflammation, and an inhaled long-acting drug called a beta-agonist (such as salmeterol) that acts by relaxing and dilating airway passages. Because corticosteroids have unwanted widespread side effects, some doctors are treating their asthma

patients with a beta-agonist, alone. This study demonstrated that treating asthma with salmeterol alone resulted in appreciable loss of disease control as assessed by the frequency of more severe asthma attacks, deleterious changes in symptoms, and signs of inflammation in the saliva. An editorial accompanying this publication recommended that the current guidelines for managing asthma be adhered to and that long-acting beta-agonists should not be used alone. [secondary – treatment]

Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr., Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T, Drazen JM, Ford JG, Israel E, Martin RJ, Mauger EA, Nachman SA, Spahn JD, and Szeffler SJ: Asthma Clinical Research Network of the National Heart, Lung and Blood Institute: long-acting β_2 -agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. The Journal of the American Medical Association 285: 2583-2593, 2001.

Orange Juice Alters the Metabolism of Certain Drugs. When grapefruit or sour orange juices are taken orally simultaneously with a number of different drugs, the concentrations and excretion times of the drugs may increase. A group of chemicals known as furocoumarins present in these juices have now been shown to achieve these effects by inhibiting the activity of the intestinal form of the enzyme cytochrome P450-3A4, which is involved in the normal disposal by the body of many different drugs. Understanding the effect of everyday nutrients on the potency of common medications will protect patients from potentially serious adverse events. [secondary – prevention]

Malhotra S, Bailey DG, Paine MF, and Watkins PB: Seville orange juice-felodipine interaction: comparison with dilute grapefruit juice and involvement of furocoumarins. Clinical Pharmacology and Therapeutics 69: 14-23, 2001.

Improving Understanding of Placenta Development. The outcome of human pregnancy depends on specialized placental cells that physically connect the embryo/fetus to the mother. As these cells grow into the uterine wall they sense increasingly higher levels of oxygen, which make them change shape and form blood vessels that connect with the mother's blood vessels, thus serving to supply the growing fetus with oxygen through the placenta. To better understand this process, these specialized cells were grown in the laboratory, under high and low oxygen levels. Hundreds of proteins from cells grown under these different conditions were separated all at once to see whether the difference in oxygen level affected how much of each protein was present. The proteins that changed were identified using new mass spectrometry techniques. These sophisticated new methods identified many proteins that may be critical in unraveling the reasons behind pregnancy complications. Experiments like this one not only advance medicine, but also provide a setting for further development of state-of-the-art analytical technologies for other extraordinarily complex experiments in the post-genomic era.

Hoang VM, Foulk R, Clauser K, Burlingame AL, Gibson BW, and Fisher SJ: Functional proteomics: examining the effects of hypoxia on the cytotrophoblast protein repertoire. Biochemistry 40: 4077-4086, 2001.

Body Position Alters Heart Rate. A common disorder (the neuropathic postural tachycardia syndrome) that primarily affects young women is characterized by lightheadedness, dimmed vision, confusion, anxiety, skin discoloration and a dramatic increase in heart rate that all occur upon assuming a standing position. Investigators at the Vanderbilt University General Clinical Research Center determined that a pathologic and ineffective accumulation of the hormone norepinephrine, which is released by certain nerve endings, occurs due to deficient nerve connections in the legs. Thus, the investigators recommend that patients afflicted with this syndrome be treated with increased fluid and salt intake, a mineralocorticoid hormone, regular exercise, and support stockings. [secondary – treatment]

Jacob G, Costa F, Shannon JR, Robertson RM, Wathen M, Stein M, Biaggioni I, Ertl A, Black B, and Robertson D: The neuropathic postural tachycardia syndrome. The New England Journal of Medicine 343: 1008-1014, 2000.

A Role for “Junk DNA:” Functional Significance of Repetitive DNA Elements in Eukaryotic Genomes. Only 2 percent of the human genome contains DNA that encodes functional proteins, while more than 50 percent is composed of repetitive DNA elements that were long thought to be non-essential and non-functional pieces of genetic material in the eukaryotic genomes. Computational research supports the discovery that repetitive DNA elements can in fact affect the organization and evolution of a genome, can influence cellular activities by acting as recombination hot spots, and, when integrated in or near an active gene, can affect the control of gene expression. Thus, while genetic variability in a species is typically a direct result of mutation or recombination between homologous chromosomes, an elucidation of the functional roles of repetitive DNA elements is significant in that it demonstrates the existence of alternate molecular mechanisms for creating genetic diversity.

Makalowski W: Genomic scrap yard: how genomes utilize all that junk. Gene 259: 61-67, 2000.

Genomic Analysis of Radiation-resistant Bacterium: A Model Organism for Understanding Mechanisms of DNA Damage and Repair. The complete genome of *Deinococcus radiodurans*, a highly radiation- and desiccation- resistant bacterium, has been sequenced and submitted to NIH's GenBank database, and is available for searching and analysis through NIH public Web services. Using a variety of bioinformatics tools developed at NIH, a group of NIH scientists has performed a detailed comparative analysis of the *D. radiodurans* genome to other microbial genomes. This comparison considered basic metabolic pathways, energy production mechanisms, DNA replication and repair mechanisms, systems for protein synthesis, and the structural properties of the proteins produced. This elucidation of the basic biological functions enables scientists to make functional predictions that can be tested experimentally. Given its unusual phenotype, *D. radiodurans* is useful in that it not only serves as a model organism for understanding the mechanisms of DNA damage and repair, but a knowledge of its basic biology can also lead to the development of genetically modified strains that can be utilized for the removal and /or stabilization of radioactive waste in the environment.

Makarova KS, Aravind L, Wolf YI, Tatusov RL, Minton KW, Koonin EV, and Daly MJ: Genome of the extremely radiation-resistant bacterium *Deinococcus radiodurans* viewed from the perspective of comparative genomics. Microbiology and Molecular Biology Reviews 65: 44-79, 2001.

Bioinformatics Tools Provide Insight into the Mechanisms of Genome Evolution and Bacterial Pathogenesis. The complete genomes of *Helicobacter pylori* and *Chlamydia pneumoniae*, two bacterial pathogens that affect humans, have recently been deposited in GenBank. These genomic sequences are available to the public through NIH Web services. NIH scientists have also performed a comparative analyses of these two genomes that highlights important features of pathogen evolution. *H. pylori* causes gastritis, ulcers and certain types of intestinal cancers. *C. pneumoniae* has been linked to respiratory ailments such as bronchitis, pneumonia and, in some cases, atherosclerosis. Using bioinformatics tools developed at NIH, a team of NIH scientists conducted an evolutionary analysis of these bacterial genomes, focusing on gene families encoding proteins of possible antigenic significance. Their results showed evidence that gene conversion played an important role in the evolution of outer membrane proteins. Gene conversion is a process in which one area of the genome of an organism overwrites another, and is thought to be an important mechanism by which bacterial pathogens create new proteins involved in their attack on a host organism. These findings are important for enhancing our understanding of the evolution and organization of these bacterial genomes, but they may also have significant potential for developing effective medical treatments for infections associated with these pathogens.

Jordan IK, Makarova KS, Wolf YI, and Koonin EV: Gene conversions in genes encoding outer-membrane proteins in *H. pylori* and *C. pneumoniae*. Trends in Genetics 17: 7-10, 2001.

Multilateral Initiative on Malaria. NIH has led an international effort to provide malaria researchers in Africa with full access to the Internet and the resources of the World Wide Web. This project began with NIH's leadership in the Multilateral Initiative on Malaria in which African scientists identified electronic communication and access to scientific information as critical in the fight against the devastating and economically debilitating effects of malaria in developing countries. Results at the completion of the Alpha Phase and Phase 1: researchers at the Malaria Research and Training Center in Bamako, Mali, are connected by radio waves to their local Internet Service Provider and their colleagues at the CDC/KEMRI and Wellcome/KEMRI sites in Kenya now fully connected via satellite for data, voice, and image. Phase 2 comprises two sites in Ghana which also have full Internet connectivity – Noguchi Institute in Accra and the Navrongo Health Research Center; both sites are engaged in a clinical trial for a malaria vaccine. Additionally three sites in Tanzania joined the network from the National Institute of Medical Research headquarters in Dar es Salaam, and at two remote research sites engaged in malaria control efforts in Ifakara and Amani. Another satellite link was put in place in Nairobi, Kenya, and a fourth Kenya site was added as part of Phase 3 at an isolated research station in Mbita Point. Phase 3 will be completed in Fall 2001 with the installation of new satellite sites at Blantyre, Mawawi in support of a pediatric malaria project, and at Entebbe, Uganda. Partners, in addition to the NIH, included the Centers for Disease

Control and Prevention, Wellcome Trust, World Bank, USAID, Naval Institute of Medical Research, and Walter Reed Army Institute of Research.

<http://www.mimcom.net/>

Royall J, Siegel E, and Bennett M: Wires, webs, and MIM-Com.Net. African Journal of Medicine (in press 2001).

Siegel E, Royall J, and Bennett M: Enhancing communications and connectivity in Africa: the multilateral initiative on malaria (mim) model. MEDINFO 2001 Proceedings 2001.

Understanding Aromatase in Breast Cancer. Many breast cancers are fed by estrogen, which is made from other hormones in the presence of the enzyme aromatase. To reduce estrogen levels, drugs that turn off aromatase are given to women with breast cancer. However, these drugs are not specific to the tumor tissue, so they reduce estrogen levels throughout the body – a problem, as estrogen plays an important role in normal body functioning. Past research has shown that the biological switch that turns on aromatase is different in cancer cells than in normal cells. Researchers have recently discovered that a molecule secreted by the tumor itself is responsible for activating aromatase. If a drug could be designed to inhibit this molecule, it would prevent the biological switch from being turned on and stop aromatase production only in tumor cells, not normal ones, thus allowing estrogen to act normally in other parts of the body and potentially reducing the toxicity of treatment. [secondary – treatment]

Zhou J, Gurates B, Yang S, Sebastian S and Bulun SE: Malignant breast epithelial cells stimulate aromatase expression via promoter II in human adipose fibroblasts: an epithelial-stromal interaction in breast tumors mediated by CCAAT/enhancer binding protein beta. Cancer Research 61: 2328-2334, 2001.

Markers for the Blood Vessels of Human Cancers. Most human cancers are maintained by an internal blood supply, which is provided by new blood vessels grown by the tumor. A major endeavor of cancer research and the pharmaceutical industry is to design drugs to inhibit such vessels; however, the basic biology of these vessels is not well understood. Researchers have used serial analysis of gene expression (SAGE), a technique for analyzing gene expression (full use of the information in a gene leading to the production of a protein), to analyze the endothelium (innermost cells) of the blood vessels in human cancers. These researchers identified a panel of tumor endothelial markers and found that most of these genes are expressed in both wound healing and cancer cells, showing that the blood vessels of tumors are not very different from other new vessels that the body normally makes. But such markers could prove immensely valuable in delivering drugs to the tumor, imaging the tumor for diagnostic or monitoring purposes, and perhaps targeting this blood supply directly to help impair the tumor itself.

St Croix B, Rago C, Velculescu V, Traverso G, Romans KE, Montgomery E, Lal A, Riggins GJ, Lengauer C, Vogelstein B, and Kinzler KW: Genes expressed in human tumor endothelium. Science 289: 1197-1202, 2000.

A Functional Atlas for *Caenorhabditis elegans*. *Caenorhabditis elegans*, a microscopic roundworm, is a useful model for scientists because it matures within days and its genetics are easily studied. Researchers are currently identifying all of *C. elegans*' genes; and once this effort is complete, the proteins encoded by the genes will be analyzed to identify their function. This is the first comprehensive effort to catalog protein interactions in eukaryotic organisms; it may offer insight into the functioning of genes and proteins in higher organisms, including humans.

Reboul J, Vaglio P, Tzellas N, Thierry-Mieg N, Moore T, Jackson C, Shin-i T, Kohara Y, Thierry-Mieg D, Thierry-Mieg J, Lee H, Hitti J, Doucette-Stamm L, Hartley JL, Temple GF, Brasch MA, Vandenhaute J, Lamesch PE, Hill DE, and Vidal M: Open-reading-frame sequence tags (OSTs) support the existence of at least 17,300 genes in *C. elegans*. Nature Genetics 27: 332-336, 2001.

Vidal M: A biological atlas of functional maps. Cell 104: 333-339, 2001.

Clues to Cancer Recurrence. Cancer researchers have long puzzled over the mechanisms by which malignant tumors recur after cancer treatment. For some time they have known that cancer cells possess one or more mechanisms by which to suppress the body's immune response, thereby escaping identification by the immune system. Now a study with mice has implicated a protein called interleukin 13 (IL-13), which is produced by specialized cells of the immune system known as natural killer T lymphocytes (NK T cells). The investigators found both IL-13 and NK T cells to be necessary for the suppression of the immune system's ability to detect tumors in mice. Conversely, tumors were prevented from recurring when IL-13 was blocked or NK T cells were eliminated. These findings suggest a new approach to cancer immunotherapy that can be used either by itself, to allow the immune system to respond to and eliminate the patient's tumor, or with cancer vaccines to enable them to work more effectively. Such approaches could lead to successful treatments for a number of types of human cancer.

Terabe M, Matsui S, Noben-Trauth N, Chen H, Watson C, Donaldson DD, Carbone DP, Paul WE, and Berzofsky JA: NKT cell-mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway. Nature Immunology 1: 515-520, 2000.

Chromosomal Instability in Cancer. Cancer is thought to be caused by the long-term accumulation of small genetic changes. These changes include the addition or deletion of pieces of a cell's chromosomes, where the genetic material resides. Researchers examined a number of very small colorectal tumors and found chromosomal changes in many of them; the fact that the changes were found in such small tumors implies that they occur very early in the progression from normal cells to cancer cells. The findings are consistent with observations about chromosomal instability in other cancers, including stomach cancer and early-stage cancer of the esophagus. Taken together, all of these studies support the idea that chromosome instability is an early component of human neoplasia in general.

Shih IM, Zhou W, Goodman SN, Lengauer C, Kinzler KW, and Vogelstein B: Evidence that genetic instability occurs at an early stage of colorectal tumorigenesis. Cancer Research 61: 818-822, 2001.

Protein Indicates Double-stranded DNA Breaks. DNA is a double-stranded molecule; as long as one strand remains intact, information can be copied from it to the other strand. However, double-stranded breaks (DSBs) often occur in which both strands are destroyed over a variable area. Double-stranded breaks can be programmed by the cell or can occur as the result of radiation or other damage. Researchers have found that a specific protein, H2AX, is altered near the site of a break, and they developed an antibody that visualizes the location of the altered protein, permitting researchers for the first time to locate and study individual DNA DSBs seconds after their formation. They found that the same protein alterations occurred whether the break was programmed or unprogrammed. Their findings provide insight into the basic biology of the cell and, because DSBs may be induced by radiation, may also have significant implications for the optimum clinical delivery of ionizing radiation to patients during treatment, for identifying persons with increased sensitivity to radiation and other chemically induced DNA DSBs, and for diagnosis of patients with defective DNA DSB formation and rejoining.

Paull TT, Rogakou EP, Yamazaki V, Kirchgessner CU, Gellert M, and Bonner WM: A critical role for histone H2AX in sequential recruitment of repair factors to nuclear foci after DNA damage. Current Biology 10: 886-895, 2000.

Chen HT, Bhandoola A, Difilippantonio MJ, Zhu J, Brown MJ, Tia X, Rogakou EP, Brotz T, Bonner WM, Ried T, and Nussenzweig A: Response to RAG-mediated V(D)J cleavage by NBS1 and γ -H2AX. Science 290: 1962-1964, 2000.

Mahadevaian SK, Turner JMA, Baudat F, Rogakou EP, de Boer P, Blanco-Rodríguez J, Jasin M, Keeney S, Bonner WM, and Burgoyne PS: Recombinational DNA double-strand breaks in mice precede synapsis. Nature Genetics 27: 271-276, 2001.

Prostate Cancer in African-American Men. The rate of prostate cancer among African-American men is dramatically higher than that for other American men. The difference is so great that some researchers have proposed setting a different reference range – the range of values that are considered “normal” – for prostate-specific antigen (PSA), an early marker for the disease, for African-Americans. However, in studying this question, researchers found that the PSA values in a group of healthy middle-aged African-American men were comparable to those in a similar group of white men. The comparable PSA values may not justify using race-specific reference ranges for prostate cancer screening.

Heeringa SG, Alcsér KH, Doerr K, Strawderman M, Cooney KA, Medbery B, and Schottenfeld D: Potential selection bias in a community-based study of PSA levels for African American Men. Journal of Clinical Epidemiology 54: 142-148, 2001.

Identification of a Novel Enzyme Active in Breast Cancer. Researchers have identified a type of enzyme called matriptase that is overactive in breast cancer, as well as its cognate inhibitor (which modulates its function). Matriptase and its inhibitor are predominantly active in poorly

differentiated (high grade) human breast cancers, and are hypothesized to play a role in breast cancer growth, invasion, and/or metastasis. Ultimately, matriptase may represent a novel target for cancer diagnosis and therapy.

Lee SL, Dickson, RB, and Lin CY: Activation of hepatocyte growth factor and urokinase/plasminogen activator by matriptase, an epithelial serine protease. Journal of Biological Chemistry 275: 36720-36725, 2000.

Enyedy IJ, Lee SL, Kuo AH, Dickson RB, Lin CY, and Wang S: Structure-based approach for the discovery of Bis-benzamidines as novel inhibitors of matriptase. Journal of Medicinal Chemistry 44: 1349-1355, 2001.

Benaud C, Dickson, RB, and Lin CY: Regulation of the activity of matriptase on epithelial cell surfaces by a blood-derived factor. European Journal of Biochemistry 268: 1439-1447, 2001.

Oberst M, Anders J, Xie B, Singh B, Ossandon M, Johnson MD, Dickson RB, and Lin CY: Matriptase and HAI-1 are expressed by normal and malignant epithelial cells *in vitro* and *in vivo*. American Journal of Pathology 158: 1301-1311, 2001.

Steroid/Nuclear Receptors Function by Hit-and-Run. Steroid/nuclear receptors are proteins that play a critical role in switching on the genes that respond to hormones, such as androgen and estrogen. They are among the most important regulators of physiological processes and organ function in humans; the 49 known receptors are central to all of human biology. Aberrant function of processes mediated by these receptors are also critical in many diseases, including cancer (notably breast and prostate cancers). What has been unclear is how these proteins orchestrate the process of transcription, or replication of a cell's DNA so the cell can divide. Now scientists have discovered that, contrary to their long-held assumption that the receptor remains fixed on the gene throughout the process of transcription, it leaves the gene as the process gets under way. This finding has important implications for cell biology – the investigators believe it is likely that other receptors act in a similar way; in addition, this new understanding of how steroid receptors work may facilitate the discovery of new drugs targeted at this class of bioregulators.

McNally JG, Muller WG, Walker D, Wolford R, and Hager GL: The glucocorticoid receptor: rapid exchange with regulatory sites in living cells. Science. 287: 1262–1265, 2000.

Fletcher TM, Ryu BY, Baumann CT, Warren BS, Fragoso G, John S, and Hager GL: Structure and properties of a glucocorticoid receptor-induced chromatin transition. Molecular Cell Biology 20: 6466-6475, 2000.

National Cancer Institute press release: Scientists report advance in understanding steroid receptors. 2001.

Szuroni P: Steroid receptors hit and run. Science 287: 1165, 2000.

Source of Gene Mutations Linked to Cancer. When tissues become overloaded with oxyradicals – by-products produced by the body's breakdown of amino acids and fats – the DNA in cells can become damaged in ways that can lead to cancer. Scientists have recently pinpointed oxyradical-induced mutations in the p53 gene, which normally acts as a tumor

suppressor. These mutations occur at an early stage in the development of liver and colon cancer. From these findings, it may one day be possible to predict a person's risk of these cancers and to target therapy that will prevent or interrupt the formation of cancer.

Hussain SP, Amstad P, Raja K, Ambs S, Nagashima M, Bennett WP, Shiels PG, Ham AJ, Swenberg JA, Marrogi AJ, and Harris CC: Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. Cancer Research 60: 3333–3337, 2000.

Hussain SP, Raja K, Amstad PA, Sawyer M, Trudel LJ, Wogan GN, Hofseth LJ, Shields PJ, Billiat TR, Trautwein C, Hohler T, Galle PR, Phillips DH, Markin R, Marrogi AJ, and Harris CC: Increased p53 mutation load in nontumorous human liver of Wilson disease and hemochromatosis: oxyradical overload diseases. Proceedings of the National Academy of Sciences U S A 97: 12770–12775, 2000.

Autoantigens in Sjögren's Syndrome. Sjögren's syndrome is a chronic autoimmune disease in which the affected individual generates an anti-self immune response leading to inflammation within tissues and organs and, in particular, dysfunction of the salivary and lacrimal (tear) glands. Although the mechanisms of tissue damage and organ dysfunction remain unclear, the protein cleaving enzymes granzyme A and granzyme B (of cytotoxic lymphocytes [white blood cells]) are believed to be critically involved. NIH-funded researchers have provided in vitro evidence that granzyme B can fragment salivary gland cell membrane structures into target antigens that induce an autoimmune antibody response. They suggest that this enzymatic pathway to production of autoantigens may reflect the initiating events of Sjögren's syndrome.

Nagaraju K, Cox A, Casciola-Rosen L, and Rosen A: Novel fragments of the Sjögren's syndrome autoantigens α -fodrin and type 3 muscarinic acetylcholine receptor are generated during cytotoxic lymphocyte granule-induced cell death. Arthritis and Rheumatism (in press 2001).

Effect of Interleukin -1 β in Periodontitis. The inflammatory cytokine interleukin -1 β (IL -1 β) has been strongly implicated in periodontal tissue destruction. It potently stimulates bone resorption and biochemical reactions that are directly relevant to periodontitis; its levels are elevated in diseased periodontal tissues, and its tissue levels correlate with episodes of active periodontal destruction. Numerous cell types, including macrophages, fibroblasts, polymorphonuclear leukocytes and monocytes, produce IL -1 β in response to microbial stimuli. NIH-funded scientists compared the IL -1 β responses of blood monocytes from adult periodontitis patients who exhibited the genetic periodontitis disease susceptibility trait (PST) with patients who lacked this trait. They found marked individual variation in IL -1 β production within both groups and concluded that genetic sites other than the PST locus are also important regulators of monocyte IL -1 β responses.

Mark LL, Haffajee AD, Socransky SS, Kent RL Jr, Guerrero D, Kornman K, Newman M and Stashenko P: Effect of the Interleukin—1 genotype on monocyte IL -1 β expression in subjects with adult periodontitis. Journal of Periodontal Research 35: 172-177, 2000.

Gene Inhibits Invasion and Metastasis of Cancers. The invasion and metastasis of cancer cells requires the destruction of surrounding connective tissue by specific enzymes. One of these enzymes is MMP-9. NIH-funded scientists conducted research that demonstrated a novel mechanism by which MMP-9 mediated metastasis may be inhibited. The *KiSS-1* gene has previously been shown to suppress metastasis. This research is the first report that *KiSS-1* down-regulates MMP-9 expression, a finding that explains, at least in part, the mechanism by which *KiSS-1* inhibits invasion and metastasis of cancers. The biochemical basis for this event, including the identification of participating proteins, has been defined.

Yan C, Wang G, and Boyd DD: KiSS-1 represses 92-kDa type IV collagenase expression by down-regulating NF- κ B binding to the promoter as a consequence of I κ B α -induced block of p65/p50 nuclear translocation. Journal of Biological Chemistry 276: 1164-1172, 2001.

New X-linked Recessive Immunodeficiency Defined. Hypohidrotic ectodermal dysplasia (HED) is a congenital disorder of teeth, hair and sweat glands that is usually inherited as an X-linked recessive trait. NIH researchers have recently identified a novel X-linked disorder involving HED and immune deficiency (HED-ID). Sequence analysis in four affected families revealed mutations in the carboxy-terminal end of the IKK-gamma protein. Complete loss of IKK-gamma function has previously been shown to result in familial incontinentia pigmenti, an X-linked dominant trait that affects females by causing variable defects of skin, hair, teeth, brain and eye, and is lethal in males. Less severe mutations result in HED-ID, an X-linked recessive immunodeficiency syndrome, distinct from other types of HED and immunodeficiency syndromes. These results suggest that the development of ectodermal appendages such as teeth, hair, and sweat glands, is mediated through a tumor necrosis factor receptor-like signaling pathway in which the IKK-gamma protein plays a significant role.

Zonana J, Elder ME, Schneider LC, Orlow SJ, Moss C, Golabi M, Shapira SK, Farndon PA, Wara DW, Emmal SA, and Ferguson BM: A novel x-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (*NEMO*). American Journal of Human Genetics 67: 1555-1562, 2000.

Potential Role of Bone Proteins in Cancer. Metastatic cancer cells, like the cells of the developing placenta, are invasive and in order to survive, must evade detection as “non-self” and consequently avoid destruction by the complement pathway of the body’s immune system. NIH scientists have studied two bone-related proteins, bone sialoprotein and osteopontin, both of which are expressed by many primary tumors. They found that both proteins form complexes with the complement system’s Factor H, a key regulating substance for complement-mediated cell destruction. Their laboratory studies have shown that each of these proteins can prevent destruction of mouse leukemia cells by the complement system, and consequently may protect cancers such as breast, prostate, and myeloma (bone marrow) as they invade normal tissues.

Fedarko NS, Fohr B, Robey PG, Young MF, and Fisher LW: Factor H binding to bone sialoprotein and osteopontin enables tumor cell evasion of complement-mediated attack. Journal of Biological Chemistry 275: 16666-16672, 2000.

Bacterial Interactions Within Dental Plaque. For quite some time, scientists have known that bacteria – including dental bacteria – can adhere to surfaces and form a slimy, slippery coat. These bacterial biofilms are prevalent on most wet surfaces in nature (including teeth) and grow in complex, multi-species communities. The formation of these communities and their inherent resistance to antimicrobial agents are at the root of many persistent and chronic bacterial infections. NIH scientists studied the interspecies cooperation of three oral bacteria found in humans, *Streptococcus oralis*, *Actinomyces naeslundii*, and *Streptococcus gordonii*, which are known to play a role early in the formation of dental plaque. The researchers found that only *S. gordonii* can grow using saliva as the sole source of its nutrients, while the other two – *S. oralis* and *A. naeslundii* – gain this ability when they cluster together. The interdependent association enables the bacteria to flourish where neither could survive on its own. Insight into bacterial interactions within early developing dental plaque may lead to noninvasive interventions to prevent the formation of destructive bacterial communities.

Palmer RJ Jr, Kazmerzak K, Hansen MC, and Kolenbrander PE: Mutualism versus independence: strategies of mixed-species oral biofilms in vitro using saliva as the sole nutrient source. Infection and Immunity 69: 5794-5804, 2001.

Self-Assembly Properties of Recombinant Engineered Amelogenin Proteins. In nature, the full structure of composite materials, such as bone, tooth structures, and skin, is made through hierarchical self-assembly on organic templates that direct the positioning of inorganic components. The protein amelogenin forms the basic building blocks of the dental enamel structural framework. The structure is determined by amelogenin protein interactions that lead to the self-assembly process. The molecular assembly of amelogenin protein has been assumed to be critical for the function of this structural protein during enamel formation. NIH researchers used a series of recombinant engineered amelogenins to determine that the processing of the amelogenins along with local pH and protein concentration affects the self-assembly process in a stepwise and controlled manner which in turn controls the maturation of the enamel. The utilization of engineered recombinant amelogenin has provided insight into the domains that contribute to protein-protein interactions, and hence to amelogenin nanosphere self-assembly. This has led to a better understanding of the role of amelogenin protein during enamel formation and maturation.

Moradian-Oldak J, Paine ML, Lei YP, Fincham AG, and Snead ML: Self-assembly properties of recombinant engineered amelogenin proteins analyzed by dynamic light scattering and atomic force microscopy. Journal of Structural Biology 131: 27-37, 2000.

The Structure of Cell Membrane Water Channels. One of the most basic requirements of a cell is the regulation of salt and water movement across its outer membrane. The aquaporin family of membrane proteins is commonly found in tissues such as the corneal endothelium that require high rates of fluid transport and provide pathways for water movement across membranes. Scientists have reconstituted highly purified human aquaporin-1 (AQP-1) into

membrane crystals and have defined its structure at a resolution of several angstroms. The atomic model of AQP-1 indicates that in the center of the membrane, the channel is large enough for a single water molecule but too small for larger ions and solutes. The arrangement of specific amino acids suggests a minimal energy barrier for water but not for charged species such as protons and that accounts for the high selectivity of AQP-1 for water.

Murata K, Mitsuoka K, Hirai T, Walz T, Agre P, Heymann JB, Engel A, and Fujiyoshi Y: Structural determinants of water permeation through aquaporin-1. Nature 407: 599-605, 2000.

Suppression of Specific Molecular Targets Improves the Success Rate of Corneal Transplants. Although most corneal transplants are successful, approximately 20 percent fail due to immunologic rejection of donor tissue. Evidence is accumulating that host tissues at the transplant site increase the concentration of certain molecules, such as tumor necrosis factor- α and interleukin-1, that are responsible for recruiting the immune and inflammatory cells that cause rejection. Specific inhibitors of these molecules can be used therapeutically to suppress the immune response and ultimately lead to greater success of grafts. [secondary – treatment]

Qian Y, Dekaris I, Yamagami S, and Dana MR: Topical soluble tumor necrosis factor receptor type I suppresses ocular chemokine gene expression and rejection of allogeneic corneal transplants. Archives of Ophthalmology 118: 1666-1671, 2000.

Yamada J, Zhu S, Streilein JW, and Dana MR: Interleukin-1 receptor antagonist therapy and induction of anterior chamber-associated immune deviation-type tolerance after corneal transplantation. Investigative Ophthalmology and Visual Science 41: 4203-4208, 2000.

Genetic Ocular Disease of Native Americans. Hereditary benign intraepithelial dyskeratosis (HBID) is a rare autosomal dominant disorder first described over 40 years ago in Native Americans in North Carolina. With onset at birth, affected individuals have tissue growth on the conjunctiva, the membrane that covers the outer surface of the eye and the back side of the eyelids. Although these growths can interfere with vision, they may also give the eye a “bloodshot” appearance that stigmatizes affected individuals in employment and social interactions, where it is assumed that drug or alcohol abuse is the cause. Using linkage analysis of two large, affected families, scientists have localized the HBID gene to chromosome 4, and will likely identify the specific gene in the near future. Although the disease is rare, knowledge about the gene will not only lead to a cure for HBID, but to a greater understanding of conjunctival epithelial cell growth.

Allingham RR, Seo B, Rampersaud E, Bembe M, Challa P, Liu N, Parrish T, Karolak L, Gilbert J, Pericak-Vance MA, Klintworth GK, and Vance J: A duplication in chromosome 4q35 is associated with hereditary benign intraepithelial dyskeratosis. American Journal of Human Genetics 68: 491-494, 2001.

Lens Cell Survival. The lens is a dense, compact structure containing two cell types: epithelial cells and fiber cells. Fiber cells are terminally differentiated, so the lens is dependent on a thin

layer of metabolically active epithelial cells for its health and survival. This is particularly important, because lens cells survive for the life of the individual. Until recently, factors that maintain lens cell survival have not been understood. A recent report has characterized one factor called LEDGF (lens epithelium-derived growth factor). Results suggest that this factor may work by stimulating the synthesis of the stress response proteins hsp27 and α -B-crystalline. LEDGF appears to have the ability to promote the survival of a wide range of cells. In a second study, scientists used LEDGF to rescue degenerating photoreceptors in rat models of retinal degeneration. Data from this study suggested that such rescue is effected through stress-related protection. These findings open the possibility that this factor could have far reaching therapeutic potential for ocular diseases caused or exacerbated by environmental stresses.

Singh DP, Ohguro N, Kikuchi T, Sueno T, Reddy VN, Yuge K, Chylack LTJr, and Shinorara T: Lens epithelium-derived growth factor: effects on growth and survival of lens epithelial cells, keratinocytes, and fibroblasts. Biochemical and Biophysical Research Communications 267: 373-381, 2000.

Machida S, Chaudhry P, Shinohara T, Singh DP, Reddy VN, Chylack, LT Jr, Sieving PA, and Bush R: Lens epithelium-derived growth factor promotes photoreceptor survival in light-damage and RCS rats. Investigative Ophthalmology and Visual Science 42: 1087-1095, 2001.

A World of Color. Perceptually, we use color information in the visual environment to discriminate objects by their hue and to identify color boundaries. Color information is encoded as electrical signals in the retina of the eye. Initially, this information is transmitted to two central structures in the brain, the lateral geniculate nucleus (LGN) in the thalamus, and then to the primary visual cortex (V1). Many additional neuronal connections are made from V1 in the brain to process this information further. The retina and the LGN have nerve cell populations sensitive to color modulation, but the role of the V1 in visual processing has been unclear until now. The accepted view has been that color processing occurs in higher visual cortical areas and that the cells in the V1 neurons are generally unresponsive to color. Recent work in macaque monkeys has reevaluated color processing in V1 by studying single neuron responses to color patterns and luminance. These studies have found that many neurons respond robustly to color signals in V1, both to luminance and to preferred color. Contrary to the prevailing view, the primary visual cortex appears to have a crucial role in how we perceive our rich, colorful environment.

Johnson EN, Hawken MJ, and Shapley R: The spatial transformation of color in the primary visual cortex of the macaque monkey. Nature Neuroscience 4: 409-416, 2001.

Sight and Consciousness. Most visual information that reaches our eyes does not reach the level of our visual awareness. How does the brain select certain inputs for access to consciousness? Recent research on this question has focused on a phenomenon in the visual system called binocular rivalry. When two very different patterns are presented to the eyes, one does not see a blending of the patterns, rather our perception alternates between the two patterns. The neural basis for binocular rivalry has been controversial. Vision researchers recently measured activity in the human visual cortex during binocular rivalry using functional magnetic resonance imaging. They focused these measurements on a small part of the visual cortex that

receives input from the part of visual space corresponding to the so-called blind spot, which receives input from only one of the two eyes. This patch of cortex corresponds to the representation of the blind spot, a part of the retina that lacks photoreceptors. The data from this experiment shows that when the blind spot becomes perceptually dominant, neural activity in the cortical blind spot is suppressed. Since neurons in this cortical location receive input only from the other eye, that input must be inhibited in the earliest stages in the cortical visual processing stream (the primary visual cortex). Thus, binocular rivalry appears to result from competition between monocular neurons at the earliest stages of visual processing. This early competition is ultimately reflected in our conscious experience of only one of the two rival visual stimuli.

Tong F, and Engel SA: Interocular rivalry revealed in the human cortical blind spot representation. Nature 411: 195-198. 2001.

New Target for Therapy in Age-related Macular Degeneration. Vascular endothelial growth factor (VEGF) has been shown to play a major role in stimulating the formation of new blood vessels (neovascularization) in the retina. But the role of VEGF in choroidal neovascularization (CNV), which occurs in the blinding disease age-related macular degeneration, is less clear. Recent studies in a mouse model of CNV have demonstrated that inhibiting certain properties or activities of the VEGF receptor protein results in almost complete inhibition of CNV. The identification of molecular factors involved in a pathologic process such as ocular neovascularization makes it possible to design effective new drug treatments.

[secondary – treatment]

Kwak N, Okamoto N, Wood JM, and Campochiaro PA: VEGF is major stimulator in model of choroidal neovascularization. Investigative Ophthalmology and Visual Science 41: 3158-3164, 2000.

Phagocytosis Pathway Dysfunction in Human Retinal Disease. The Royal College of Surgeons (RCS) strain of rat carries a mutation in a gene, MERTK, that is associated with defective metabolic processes and subsequent retinal dystrophy. Scientists have recently screened a similar human gene (a homologue) in DNA samples from individuals with various retinal diseases. Three individuals with retinitis pigmentosa carried mutations in the MERTK gene associated with a loss or reduction of MERTK function. These patients exhibited severe and progressive retinal disease similar to that seen in the RCS animal model. With early intervention it may be possible to apply the body of knowledge gained from model therapy studies of the RCS rat to benefit people with related retinal diseases.

Gal A, Li Y, Thompson DA, Weir J, Orth U, Jacobson SG, Apfelstedt-Sylla E, and Vollrath D: Mutations in *MERTK*, the human orthologue of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa. Nature Genetics 26: 270-271, 2000.

Hearing and Looking. Many objects in the real world present multiple sensory attributes. For example, an object may both be seen and heard. The brain is able to determine that both the sound and the light originate from the same object, even though neural processing of spatial information by the visual and auditory systems is very different: Visual space is encoded at the level of the retina and must initially be represented in an eye-centered reference frame. In the auditory system, the location of a sound source is deduced from differences in sound arrival time and pressure level across the two ears, and is initially represented in a head-centered reference frame. At some point in the nervous system, these two reference frames must be aligned in order to create a unified percept of the single object. Recently, scientists have directly measured the responses of single neurons to noise stimuli in monkeys that were looking to the left, to the right, or straight-ahead. The results indicated that eye position modulates the responses of neurons to sound. At the level of the inferior colliculus, where auditory stimuli converge and are then relayed to the thalamus, auditory coordinates have already been transformed towards an eye-centered frame of reference. Why should auditory information be converted into an eye-centered reference frame? The answer may be that it is critical to be able to compare visual and auditory information. Localizing sounds is more difficult than localizing visual stimuli, and it appears that the brain relies on visual signals to help interpret auditory inputs. Thus, vision may help provide the necessary feedback for auditory learning to take place.

Groh JM, Trause AS, Underhill AM, Clark KR, and Inati S: Eye position influences auditory responses in primate inferior colliculus. Neuron 29: 509-518, 2001.

How do We Know that We've Seen? Of all human senses, vision is perhaps the most dominant in shaping our perceptions of the world. Yet little is known about the nature of the neural processing that allows one to know that one has seen a particular object. Two hypotheses have been postulated about how brain activity mediates such “visual awareness”. There might be a class of neurons or neural pathways whose activity mediates awareness. Alternatively, awareness might be the result of specific forms of neuronal activity. Scientists have recently used an experimental technique called transcranial magnetic stimulation (TMS) to study signaling in the brain of normal, awake humans during perception of moving objects. They found feedback from specific visual areas of the brain was early and critical for awareness of motion. Thus, there do not appear to be “awareness-dedicated neurons”. Instead, awareness appears to be modulated by perceptual context, dependent upon back projections from higher visual areas.

Pascual-Leone A, and Walsh V: Fast backprojections from the motion to the primary visual area necessary for visual awareness. Science 292: 510-512, 2001.

Speed of Light Responses. A single photon of light can activate a single molecule of the visual pigment rhodopsin in a rod photoreceptor cell outer segment, initiating the process of vision or phototransduction. To maintain a high sensitivity to light, rod cells maintain an enormous number of rhodopsin molecules (about one billion) in their light-capturing outer segments. Although this number maximizes rod cell sensitivity, the rod cell light response rate is relatively slow. Recently, scientists have created transgenic mice in which one of the pair of rhodopsin genes has been deleted. These animals show a fifty per cent reduction in the levels of rhodopsin, but a faster recovery to a flash of light. This suggests that the extremely high packing density of rhodopsin that maximizes sensitivity, also sacrifices speed in the response to light. Rhodopsin density may limit other steps in the phototransduction process as well.

Calvert PD, Govardovskii VI, Krasnoperova N, Anderson RE, Lem J, and Makino CL: Membrane protein diffusion sets the speed of rod phototransduction. Nature 411: 90-94, 2001.

A New Ethical Framework for the Conduct of Placebo Controlled Trials. There has been significant controversy about the ethics of placebo-controlled trials. Advocates argue such trials are necessary when known interventions are not particularly effective, and there are high rates of spontaneous improvements in patients. Opponents of placebo-controlled trials counter that when a proven therapy exists it is unethical to conduct a placebo-controlled trial because denying them proven treatments will harm human research participants. This controversy has influenced the 2000 revisions of the Declaration of Helsinki. Now NIH investigators have shown that the arguments proposed by both advocates and opponents of placebo-controlled trials are seriously flawed. They offer an alternative framework for determining the ethics of placebo controlled trials arguing that they are ethical only when 1) there is a high placebo response rate, 2) patients experience spontaneous remissions, and 3) existing therapies are only partially effective or have serious side effects. When these conditions are fulfilled, placebo controlled trials are only ethical if research participants are unlikely to suffer death, irreversible morbidity, serious but reversible harms or severe discomforts. This ethical framework will provide reasonable guidance to researchers, IRBs, and funders about when it is appropriate to conduct placebo-controlled trials.

Emanuel EJ, and Miller FG: Placebo-controlled trials and active-controlled trials – a middle ground. The New England Journal of Medicine (in press 2001).

White Blood Cell Types that Have a Hand in Fighting Infections. White blood cells called neutrophils play an important role in fighting infections. Antibodies help neutrophils recognize and kill bacteria. In order for neutrophils to eat and kill bacteria they must first capture antibody-coated bacteria using a protein hand or receptor called Fc-gamma-Receptor IIIb (Fc γ RIIIb). Two different types of the Fc γ RIIIb receptors have been described: the NA1 and NA2. NA1 and NA2 are like right and left hands; there are only minor differences in how they look, but there are some important differences in what they do. The NA2 type is more common in Caucasians and African-Americans and the NA1 type is more common in Japanese and Chinese. White cells or neutrophils that have the NA1 type grab antibody-coated bacteria more

tightly than type NA2 white cells. Researchers have discovered new Fc γ RIIIb types. The new types are most similar to the NA2 and are most often found in African-Americans. Initially, researchers discovered the new types by studying genes encoding Fc γ RIIIb. Recently, researchers studied the protein structure of Fc γ RIIIb on the outside of white cells and found that the new genes produced unique proteins that were a mixture of NA1 and NA2. Most of the protein hand was like the NA2 type, but one or two fingers were like the NA1 type. These new types may help explain differences in response of people from different racial backgrounds to certain infections.

Matsuo K, Lin TI, Procter J, and Stroncek D: Variations in genes encoding neutrophil antigens NA1 and NA2. Transfusion 40: 654-661, 2000.

Matsuo K, Procter JL, Chanock S, and Stroncek DF: The expression of NA antigens in people with unusual Fc γ receptor III genes. Transfusion 41: 775-782, 2001.

HIV Infection Increases the Risk of Transmission of Herpes and Cytomegalovirus (CMV) to Sexual Partners and Newborns. Infection by herpes simplex virus and by CMV are life-long infections that may be transmitted to sexual partners and to newborns if the viruses are present in the genital tract. In newborns, infection by herpes or CMV generally causes severe brain damage or death. This study followed a cohort of women in Kenya to determine the effects of HIV infection and fluctuating hormone levels during the menstrual cycle on asymptomatic shedding of herpes virus and CMV. The presence of the virus in the cervix was determined by cervical swab samples, and PCR was used to detect the presence or absence of herpes and CMV viral DNA in the swab samples. For individual women, there was considerable variability in the percentage of days on which virus was detected, ranging from 0 percent to 33 percent for herpes and from 20 percent to 97 percent for CMV. Shedding of herpes virus did not vary significantly with menstrual cycle; however, shedding of CMV was more frequent during the latter half of the menstrual cycle. These data suggest that the risk of transmitting both viruses to sexual partners and neonates may be higher than previously recognized. Counseling strategies should take this into consideration.

Mostad SB, Kreiss JK, Ryncarz A, Chohan B, Mandaliya K, Ndinya-Achola J, Bwayo J, and Corey L: Cervical shedding of herpes simplex virus and cytomegalovirus throughout the menstrual cycle in women infected with human immunodeficiency virus type 1. American Journal of Obstetrics and Gynecology 183: 948-955, 2000.

Clinical Manifestations of HIV Infection in Thailand. Thailand is experiencing one of the largest HIV epidemics in the world. Between 1994 and 1998, over 100,000 patients with AIDS over the age of 10 years were reported. The number of cases doubled between 1994 (about 12,000) and 1998 (almost 25,000). While the scale of the epidemic is widely recognized, little research has been published on the clinical manifestations of AIDS in Thailand. Using information reported to the Thai Ministry of Health, NIH-supported scientists and trainees and their counterparts in Thailand conducted a study to assess national needs for clinical services. As in Africa and other parts of Asia, tuberculosis was the most common opportunistic infection (29 percent), followed by *Pneumocystis carinii* pneumonia (20 percent), and cryptococcal meningitis (19 percent). Fungal infections were also common. These findings suggest that significant clinical benefits might result from efforts to prevent and treat tuberculosis and fungal infections. The study also serves to illustrate that, although prevention efforts will remain essential in developing countries, effective treatment of AIDS-related opportunistic infections will become increasingly important for survivors in the future.

Chariyalertsak S, Sirisanthana T, Saengwonloey O, and Nelson KE: Clinical Presentation and risk behaviors of patients with acquired immunodeficiency syndrome in Thailand, 1994-1998: regional variation and temporal trends. Clinical Infectious Diseases 32: 955-962, 2001.

Understanding HIV-Related High-Risk Sexual Behaviors Among Women in Bogota, Colombia. Understanding prevalent sexual practices in a given population is essential for designing effective interventions for preventing HIV transmission. In Colombia, which has the third highest rate of reported AIDS cases in Latin America, HIV infections are increasing among women. Yet, little is known about women's sexual practices and behaviors in that country. NIH-funded investigators in Bogota studied the sexual practices of Colombian women in the general population and female commercial sex workers who commonly engage in high-risk sexual behaviors. Fewer than 10 percent of women in the general population reported using condoms, although among commercial sex workers this was closer to 70 percent. Other unsafe practices include intercourse during menstruation; fewer than half of the women from both groups recognized the increased risk for HIV transmission associated with blood contact during menstruation. This study provides important evidence for integration of education to reduce high-risk sexual practices among all women.

Miguez-Burbano MJ, Angarita I, Shultz JM, Shor-Posner G, Klaskala W, Duque JL, Lai H, Londono B, and Baum MK: HIV-related high risk sexual behaviors and practices among women in Bogota, Colombia. Women and Health 30 : 109-119, 2000.

HIV Protease Inhibitors Impair Fat Cell Development. Current therapy for HIV infection usually involves a multi-drug regimen known as highly active antiretroviral therapy (HAART), which includes an HIV protease inhibitor (PI). HAART has been very effective in decreasing viral load, reversing wasting, and prolonging survival in adults with HIV infection. Recently, concerns have been raised regarding the possible complications of HAART, specifically the development of a potentially serious metabolic syndrome that results in the redistribution of

body fat, abnormal lipids, and insulin resistance or diabetes. A group of scientists studying the differentiation of mouse pre-fat cells in tissue culture examined whether the PI nelfinavir inhibited the formation of new fat cells or the survival of pre-existing ones. They found that when immature cells were stimulated to differentiate, they failed to do so in the presence of the PI; when mature fat cells were treated with the drug, they died. Nelfinavir is not toxic to pre-fat cells; instead, it seems to inhibit both the differentiation of immature fat cells and to promote the death of already mature ones. Understanding the molecular basis of metabolic changes associated with HAART may lead to the development of safer, more effective anti-HIV therapies.

Dowell P, Flexner C, Kwiterovich PO, and Lane MD: Suppression of preadipocyte differentiation and promotion of adipocyte death by HIV protease inhibitors. Journal of Biological Chemistry 275: 41325-41332, 2000.

In-Utero Exposure to Diabetes Increases Offspring's Risk of Diabetes and Obesity. Babies born to mothers with diabetes have an increased risk of becoming diabetic and obese. This is a well-established correlation. Until recently, however, there was no way to determine whether the children became diabetic and obese solely due to genetic inheritance or if there was an environmental contribution from their *in-utero* exposure to diabetes. A carefully-designed study determined the contributions of *in-utero* exposure to diabetes while subtracting out the contributions of genetic inheritance. To do this, the researchers compared the incidence of diabetes and obesity in children born to the same parents when one child was born before the mother was diagnosed with diabetes, and its sibling was born after the mother's diagnosis. In this comparison, both siblings have similar genetic inheritance, but only one was exposed to diabetes in the womb. Children born after their mothers were diagnosed with diabetes were much more likely to be diabetic and obese. These results provide significant evidence that exposure to diabetes in the womb increases a child's risk of developing both diabetes and obesity, and this risk is not due to genetic inheritance alone. This information is particularly important since type 2 diabetes is increasingly occurring in younger patients, including women of reproductive age. Preventing diabetes in such women until after their child-bearing years may improve not only the health of the mother but also the health of the offspring.

Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, and Knowler WC: Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity. Diabetes 49: 2208-2211, 2000.

Genetic Influence in Obesity and the Metabolic Syndrome. Obesity is one of the fastest growing health problems in the U.S. Individuals who are overweight or obese are at increased risk for developing a number of diseases, including type 2 diabetes, hypertension, stroke, and heart disease. Obesity is a complex problem influenced by multiple genes and their interaction with the environment. This year, researchers have found evidence linking several genetic regions to obesity. Several studies had implicated a region on chromosome 10 as contributing to obesity. A recent study did a combined analysis of results from studies looking at people of European American and African-American ancestry. This analysis confirmed the findings in French and German groups that a region on chromosome 10 appears to contribute to obesity. Obesity is one component of a "metabolic syndrome" that includes increased risk of diabetes,

hypertension, dyslipidemia, and cardiovascular disease. This condition is believed to result from the interaction between abdominal fat, total body fat and resistance to the action of insulin (insulin resistance). Genetic analysis identified an area on chromosome 3 containing markers closely associated with body weight; body mass index; fat distribution determined by waist and hip circumference; insulin resistance and blood insulin levels. The latter two parameters are both strong predictors of glucose intolerance and diabetes. This study also showed that the genetic region on chromosome 3 works together with another region on chromosome 17 to produce the adverse features of obesity. The potential interrelationship between these two regions suggests that pathways regulated by genes in these areas may influence variations in total adiposity, fat patterning, and insulin sensitivity. Researchers went one step further and identified potential candidate genes within these two chromosomal regions that could play a role in the biology of the metabolic syndrome. Further research will seek to clarify the functions of proteins produced by these genes and to determine their role in the development of obesity and the metabolic syndrome.

Kissebah AH, Sonnenberg GE, Myklebust J, Goldstein M, Broman K, James RG, Marks JA, Krakower GR, Jacob HJ, Weber J, Martin L, Blangero J, and Comuzzie AG: Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. Proceedings of the National Academy of Sciences USA 97: 14478-14483, 2000.

Price RA, Li WD, Bernstein A, Crystal A, Golding EM, Weisberg SJ and Zuckerman WA: A locus affecting obesity in human chromosome region 10p12. Diabetologia 44: 363-366, 2001.

Clinical Expression of Hereditary Pancreatitis. Hereditary pancreatitis (HP), inflammation of the pancreas, is a rare disease caused by a mutation in the gene that codes for the protein cationic trypsinogen. Because it is a dominant mutation, only one copy of the mutated gene is required to have HP. However, the severity of pancreatitis is variable and only 80 percent of individuals with this mutation have clinical symptoms. This correlation led researchers to hypothesize that in addition to the mutated gene, other modifier genes or environmental factors may contribute to the onset of HP. To explore this possibility, identical twins were compared to sibling pairs and paired unrelated individuals as to the incidence of pancreatitis and the age of disease onset. This comparison revealed that factors, other than environmental or modifying genes, are necessary for the clinical expression of HP. This study provides a first step in elucidating the mechanisms of expression of HP. Once this is accomplished, new therapies to minimize the symptoms or prevent this disease can be developed.

Amann ST, Gates LK, Aston CE, Pandya A, and Whitcomb DC: Expression and penetrance of the hereditary pancreatitis phenotype in monozygotic twins. Gut 48: 542-547, 2001.

Risk Factors for Primary Biliary Cirrhosis. Primary biliary cirrhosis (PBC) is an uncommon autoimmune disease of the liver that is most often seen in women. In this disease, the patient's immune systems makes antibodies to some of their own proteins called mitochondrial antigens. This leads to the destruction of small bile ducts followed by cirrhosis of the liver and liver failure. Researchers conducted a survey of approximately 500 individuals in three groups that included PBC patients, their siblings, and their friends. Results of the survey show that PBC patients are likely to have other autoimmune diseases. Approximately six percent of patients have at least one relative with PBC, indicating that genetic factors contribute to this disease. For PBC patients, there is a higher rate of urinary tract infections and a variety of illnesses and surgeries, including tonsillectomies, suggesting an infectious etiology. A strong association between PBC and smoking raises the possibility that smoking may have an effect on the Th1 immune response that occurs with PBC. Results from this extensive study indicate that PBC is caused by the interactions of genetic and environmental factors and provide a platform from which future studies can be launched.

Parikh-Patel A, Gold EB, Worman H, Krivy KE, and Gershwin ME: Risk factors for primary biliary cirrhosis in a cohort of patients from the United States. Hepatology 33: 16-21, 2001.

Brain Activity in Patients with Irritable Bowel Syndrome. The cause of irritable bowel syndrome (IBS) is unknown. Individuals with IBS seem to have a colon that is more reactive and sensitive than usual, so it responds strongly to stimuli that would not bother most people. Stress may be a factor in the manifestation of disease symptoms. To evaluate the sensitivity and reactivity of IBS patients to stimuli, researchers measured regional brain activity of patients and healthy controls during anticipated and delivered stimulation by rectal balloon distension. Each group responded similarly to actual and anticipated stimuli. However, IBS patients exhibited altered processing of their responses. In response to aversive stimuli, IBS patients had reduced blood flow to specific circuits of the brain, as well as preferential activation in regions of the

brain that are involved in the processing of negatively charged emotional information. This study provides solid evidence of altered brain activity in patients suffering with this syndrome of unknown origin.

Naliboff BD, Derbyshire SWG, Munakata J, Berman S, Mandelkern M, Chang L and Mayer EA: Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. Psychosomatic Medicine 63: 365-375, 2001.

Gene Linked to Kidney Disease Caused by Diabetes. Kidney disease is the major cause of excess morbidity and premature mortality in people with type 1 diabetes. Previous studies suggested that, although prolonged high blood glucose levels play an important role, genetic susceptibility is required for diabetic kidney disease to occur. Recently, researchers identified a variation in the apolipoprotein E gene in type 1 diabetics that is associated with a three-times greater risk of developing kidney disease. This association first was found by doing a large, case-controlled clinical study, and was extended to a family-based association study. The latter is perhaps the most reliable method for examining associations between DNA sequence differences and specific diseases. While several previous investigations of the apolipoprotein E-diabetic kidney disease association yielded equivocal results, this study is perhaps the most definitive to date. One important next step of this research is to determine the molecular mechanisms that underlie the risk for diabetic kidney disease that is caused by the apolipoprotein gene variant.

Araki S, Moczulski DK, Hanna L, Scott LJ, Warram JH, and Krolewski AS: *APOE* polymorphisms and the development of diabetic nephropathy in type 1 diabetes: results of case-control and family-based studies. Diabetes 49: 2190-2195, 2000.

Decade of ELSI Research Conference. On January 16-18, 2001, the Ethical, Legal, and Social Implications (ELSI) Research Programs of NIH and the Department of Energy sponsored a conference to reflect on the past, present, and future of ELSI research and consider its impact on genetic research, health, and public policy. More than 400 people attended the three-day conference. Almost 90 peer-reviewed papers were presented by leading ELSI researchers on topics such as genetic privacy and discrimination; the integration of genetic technologies and information into healthcare; genetic enhancement; behavioral genetics; and genetic variation, race, and culture. The conference concluded with a town meeting during which issues raised during the conference were discussed and future topics for ELSI research were suggested.

Abstracts from conference presentations at 'A Decade of ELSI Research: A celebration of the first ten years of the ethical, legal, and social implications (ELSI) programs' Journal of Law Medicine & Ethics (supplement) 29: 1-65, 2001.

African-American Hereditary Prostate Cancer Study Network. While Caucasian men on average have a one-in-five chance of developing prostate cancer during their lifetimes, African-American men are twice as likely to develop this disease, and when they do, the disease is more

likely to be fatal. Although African-Americans have the highest incidence and mortality rates of any ethnic group in the U.S., very few African-American families have been studied for hereditary prostate cancer. However, thanks to a collaboration between the NIH, Howard University, and the National Medical Association, approximately 100 African-American families with a history of early-onset prostate cancer have been recruited to help identify specific genes involved in the disease that may be enriched in this ethnic population.

Royal C, Baffoe-Bonnie A, Kittles R, Powell I, Bennett J, Hoke G, Pettaway C, Weinrich S, Vijayakumar S, Ahaghotu C, Mason T, Johnson E, Obeikwe M, Simpson C, Mejia R, Boykin W, Roberson P, Frost J, Faison-Smith L, Meeghan C, Foster N, Furbert-Harris P, Carpten J, Bailey-Wilson J, Trent J, Berg K, Dunston G, and Collins F: Recruitment experience in the first phase of the African American hereditary prostate cancer (AAHPC) study. Annals of Epidemiology 10: S68-S77, 2000.

Powell IJ, Carpten J, Dunston G, Kittles R, Bennett J, Hoke G, Pettaway C, Weinrich S, Vijayakumar S, Ahaghotu CA, Boykin W, Mason T, Royal C, Baffoe-Bonnie A, Bailey-Wilson J, Berg K, Trent J, and Collins, F: African-American heredity prostate cancer study: model for genetic research. The Journal of the National Medical Association 93:120-123, 2001.

African-American Diabetes Mellitus Study (AADM). Type 2 diabetes is already a major health threat in populations in developed countries and this global diabetes epidemic is also rapidly taking hold in the developing world. NIH scientists are collaborating with scientists at Howard University to identify type 2 diabetes susceptibility genes. Because of the high frequency of environmental risk factors for type 2 diabetes in the African-American population, it is more productive to study genetic risk factors in West Africans, since they are thought by many anthropologists to be the founding population of modern African-Americans and have fewer dietary and nutritional confounding variables. Affected siblings and unaffected spouses are being enrolled and examined in West Africa, with three recruitment sites in Nigeria and two in Ghana. One hundred and sixty-two individuals have been enrolled and examined since the African-American Diabetes Mellitus (AADM) study began in 1997. Logistics of field examinations and specimen shipping have been successfully established. The AADM study will create a comprehensive epidemiologic and genetic resource that will facilitate a powerful genome-wide search for susceptibility genes to type 2 diabetes in populations of West African descent.

Rotimi CN, Dunston GM, Berg K, Akinsete O, Amoah A, Owusu S, Acheampong J, Boateng K, Oli J, Okafor G, Onyenekwe B, Osotimehin B, Abbiyesuku F, Johnson T, Fasanmade O, Furbert-Harris P, Kittles R, Vekich M, Adegoke O, Bonney G, and Collins, F: In search of susceptibility genes for type 2 diabetes in West Africa: the design and results of the first phase of the AADM study. Annals of Epidemiology 11: 51-58, 2001.

A Mouse Model for a Cancer Syndrome that Results in Multiple Endocrine Tumors.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant cancer syndrome characterized by multiple tumors of the parathyroid, pancreas, and pituitary. It is caused by mutations in the *MEN1* gene, which was identified by NIH scientists in 1997. Menin, the protein encoded by *MEN1*, appears to function as a classic tumor suppressor that plays a role in preventing unregulated cell division. A mouse model of MEN1 was generated to examine the cellular transitions that lead to pancreatic tumors when menin is absent. The tumor incidence

and distribution pattern in the mice correlate closely with the human MEN1 phenotype. Ultimately, the availability of a mouse model for MEN1 should be an asset for testing possible therapeutic approaches for this inherited disorder and its sporadic counterparts. [secondary – prevention]

Crabtree JS, Scacheri PC, Ward JM, Garrett-Beal L, Emmert-Buck MR, Edgemon KA, Lorang D, Libutti SK, Chandrasekharappa SC, Marx SJ, Spiegel AM, and Collins FS: A mouse model of multiple endocrine neoplasia, type 1, develops multiple endocrine tumors. Proceedings of the National Academy of Science USA 98: 1118-1123, 2001.

Usher Syndrome Type 1D. Scientists have identified a novel gene (*Cdh23*) that causes deafness in mice. It was shown that mutations in the human version of this gene are the underlying cause of Usher syndrome type 1D, which is an inherited disorder characterized by deafness, blindness, and vertigo.

Bryda EC, Kim HJ, Legare ME, Frankel WN, and Noben-Trauth K: High-resolution genetic and physical mapping of modifier-of-deafwaddler (*mdfw*) and waltzer (*Cdh23*^u). Genomics 73: 338-342, 2001.

DiPalma F, Holme RH, Bryda EC, Belyantseva IN, Pellegrino R, Kachar B, Steel KP, and Noben-Trauth K: Mutations in *Cdh23*, encoding a new type of cadherin, cause stereocilia disorganization in waltzer, the mouse model for Usher syndrome type 1D. Nature Genetics 27: 103-107, 2001.

Functional Connectivity Between Brain Areas During the Visual Processing of Word and Word-Like Stimuli. Scientists have used functional magnetic resonance imaging to show that different parts of the inferior frontal gyrus participate in different functional networks during the processing of visually presented words and word-like stimuli. These networks seem to deal with different aspects of language processing, specifically meaning and phonology (the relation of speech sounds to meaningful linguistic units).

Bokde ALW, Tagamets MA, Friedman RB, and Horwitz B: Functional interactions of the inferior frontal cortex during the processing of words and word-like stimuli. Neuron 30: 609-617, 2001.